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Sulodexide Versus Calcium Heparin in the Medium-Term Treatment of Deep Vein Thrombosis of the Lower Limbs

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ABSTRACT

Thirty adult patients with distal, monolateral deep vein thrombosis of the lower limbs were randomly treated for sixty days either with subcutaneous Ca-Heparin or with Sulodexide, administered IM for ten days and orally for fifty days. The thrombus accretion above the knee, the venous pressures of the affected leg, the clinical symptomatology, and some laboratory coagulative tests were monitored throughout the administration period. Local tolerability of the two treatments was also evaluated.

The two applied treatments evidenced a net antithrombotic activity, preventing thrombus accretion above the knee, improving with the same efficacy the venous pressures in the affected legs, and similarly reducing clinical symptoms, with a quick and statistically significant trend toward normalization. Blood fibrinogen was significantly lowered by both drugs, while only Ca-heparin yielded a prolongation of activated partial thromboplastin time. Local tolerability of treatments was better for the mainly oral Sulodexide administrations, while subcutaneous Ca-heparin often induced small, though transient, hematomas.

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Introduction

Deep vein thrombosis (DVT) of the lower limbs is a relatively common condition and may become dramatically serious when a life-threatening episode of pulmonary embolism occurs.[1,2] Injured, orthopedic, gynecologic, obstetric, and surgical subjects are at risk, but occasionally DVT occurs as a first event in healthy subjects or in patients treated by estrogens and in women taking oral contraceptives.[3-5]

The pathogenesis of thrombosis is still not completely clear, since this complex process involves at the same time the blood flow, the vessel wall endothelium, and the coagulative and fibrinolytic systems.[6] There is, however, consensus on the clinical approach to treatment of DVT of the lower limbs, ie, the correct and timely use of anticoagulant agents (first of all heparin) and of thrombolytic and fibrinolytic drugs.[7-9] Chemically heparin is an acid mucopolysaccharide related to the glycosaminoglycans (GAG) family;[10] other GAGs (including those naturally present in several organic tissues[11]) have been shown to possess, with varying intensity, anticoagulant and antithrombotic properties; some of these can be used for treatment of thrombotic disorders.

Sulodexide (INN) is a naturally occurring glycosaminoglycan, consisting of a fast-moving heparin fraction of 80% and dermatan sulphate of 20%, which is characterized by a clear-cut antithrombotic activity and is used for treatment of both venous and arterial vascular disorders with thrombotic risk.[12-21] The oral and parenteral administration of Sulodexide has been shown to enhance fibrinolysis, both in animal[22,23] and in human[24-27] models, as well as to antagonize the plasminogen activator inhibitor.[24-29] It also favorably modifies, mainly after long-term use, plasma rheology.[14,25,29-31] A recent controlled trial[32] also reported the results of a medium-term (one-year) therapy with Sulodexide, started soon after an episode of acute myocardial infarction and performed by IM route during the first month and by the oral route during the remainder period. The drug, with respect to placebo, significantly reduced total mortality, the rate of reinfarction, and the rate of formation of mural thrombi.

Sulodexide exerts a coordinated action on blood coagulation, on fibrinolysis, and on blood rheology. Its mechanism of action is, on the whole, antithrombotic, since it interacts with antithrombin III (AT III), owing to the fast-moving heparin fraction, and with heparin cofactor II (HC II), owing to the dermatan fraction. It furthermore inhibits activated factor X without influencing the activated partial thromboplastin time (aPTT) and thrombin time (TT).[33,34] Pharmacokinetic studies performed employing radioactive or nonradioactive labeled substances[35-38] pointed, for orally administered Sulodexide, to a relative bioavailability ranging between 64% and 100%. Sulodexide has been marketed for several years as ampoules for IM/IV use and as capsules for oral use, with excellent tolerability of both administration routes. Its safety, besides its evident efficacy, make this drug peculiarly apt for long-term treatments.

For this reason we wanted to compare the effects of treatment with Sulodexide—mainly performed by oral route—with the results of a classical antithrombotic therapy, ie, subcutaneous Ca-heparin, which, though being undoubtedly effective, is characterized by a varying hemorrhage risk and may be less tolerated in the long term, since an oral formulation for heparin is not available yet. For this preliminary study we selected patients presenting with thrombotic episodes located under the knee (distal DVT), notoriously bearing a lesser risk of inducing pulmonary embolism, since for the first time—to our knowledge—a treatment of the thrombotic episode was performed with orally administered Sulodexide.

Materials and Methods

The study protocol was cleared by the Ethics Committee operating at our institution. Thirty adult outpatients of both sexes, presenting with monolateral, distal DVT, were selected. The clinical diagnosis of DVT had to be confirmed by a continuous-wave (CW) Doppler test; furthermore clinical symptomatology had to be of medium intensity (mean score of single symptoms 1.5). Exclusion criteria were the following: proximal (above the knee) DVT, recent treatment with other anticoagulant or antithrombotic drugs, known hypersensitivity to mucopolysaccharides, renal or cardiovascular insufficiency of high degree, and tumor. With an open design, patients were randomly distributed between two treatment group of 15 subjects each, to be treated for two months either with Sulodexide (Vessel Due F, Alfa Wasserman S.p.a., Bologna, Italy) or with calcium heparin. Sulodexide administration scheme was: 600 lipoproteinlipase releasing units

(LRU) by IM route twice a day for ten days, then 500 LRU twice a day by oral route for the subsequent fifty days. Ca-heparin administration scheme was: 12,500 IU by SC route twice a day for ten days, then 12,500 IU once a day by SC route for the subsequent fifty days. The following items were evaluated in all patients:

- at the start of treatment and then after 10 and 60 days, the following venous pressures in the affected leg, through the CW Doppler test: clinostatic and orthostatic pressures of the posterior tibial vein and orthostatic pressure of the great saphenous vein
- at the end of the 60-day treatment period, echoduplex test to evaluate whether the thrombus had extended above the knee
- at the start of treatment and then after five, ten, thirty, and sixty days: clinical signs and symptoms of thrombosis on the affected leg (reddening, hyperthermia, pain, edema). Their presence and modifications were registered by means of the following arbitrary scores: reddening and cutaneous hyperthermia: 0 = absent; 1 = slight cutaneous reddening, slight increase in temperature at the site of the reddening; 2 = fiery red color of skin, increase in temperature at the site of the reddening and the surrounding skin; 3 = fiery red color of skin, radiating heat felt even without direct contact of the hand on the skin. Pain: 0 = absent; 1 = slight and tolerable, not interfering with normal daily activities; 2 = moderate but stressful, limiting normal daily activities; 3 = severe and disabling, preventing normal daily activities and increasing with minimal contact and/or at the slightest functional strain. Local edema: 0 = absent; 1 = slight, perimalleolar, soft, covered by healthy skin, no pain; 2 = moderate, perimalleolar or spreading to the forefoot and/or the leg, with white pitting and moderate pain on palpation; 3 = severe, with increased consistency, very painful on palpation
- at the start of treatment and then after ten and sixty days, the following laboratory tests to monitor the treatments' effectiveness: prothrombin time (PT; kit from Boehringer Mannheim, Germany); partial thromboplastin time (PTT; kit from Boehringer Mannheim, Germany); blood fibrinogen (kit from Clauss-Boehringer Mannheim, Germany)

Local tolerability of both IM and SC injections and of oral administrations was strictly monitored during the study period by specifically questioning each patient and by registering their spontaneous reports. Also the appearance of adverse events of any kind was thoroughly monitored.

To statistically evaluate the effects of the two treatments on clinical and instrumental parameters, the analysis of variance for repeated measures (ANOVA), testing a two-factor model, was carried out. On the other hand, after performing the Mauchly test for sphericity (result not significant), the univariate approach was applied to test the effect of time on each laboratory parameter. Then, the Student-Neuman-Keuls post-hoc test was used for comparison of means with the baseline value. A P value <0.05 was considered statistically significant.

Results

The thirty consecutive outpatients (22 women, 8 men) had an average age of fifty-nine years (range: thirty-five to seventy-five). All were suffering from monolateral tibiopopliteal venous thrombosis confirmed by the CW Doppler test. The two treatment groups were homogeneous in regard to sex and age distribution, the frequency and severity of attending symptoms prior to starting treatment, and the results of initial laboratory tests.

At completion of the two treatments, no case of thrombus accretion above the knee could be detected. Also the behavior of venous pressures was nearly always superimposable in the two groups: a clear-cut and statistically significant ($P<0.001$ for both groups) pressure decrease was in fact always evident at the end of treatments (Figure 1).

All monitored symptoms were progressively and similarly reduced by treatments, which yielded, already after the first ten-day phase at higher dosages, a pronounced reduction of scores (Figure 2). Only in the Sulodexide-treated patients was a marked decrease in hyperthermia registered at the first check after five days, with statistical significance by the Student's t test ($P<0.05$), vs heparin-treated patients. During the second administration phase at lower doses, symptoms further improved, so that after sixty days, reddening, hyperthermia, and pain had completely disappeared, while a negligible edema was still present in some patients of the two subgroups.

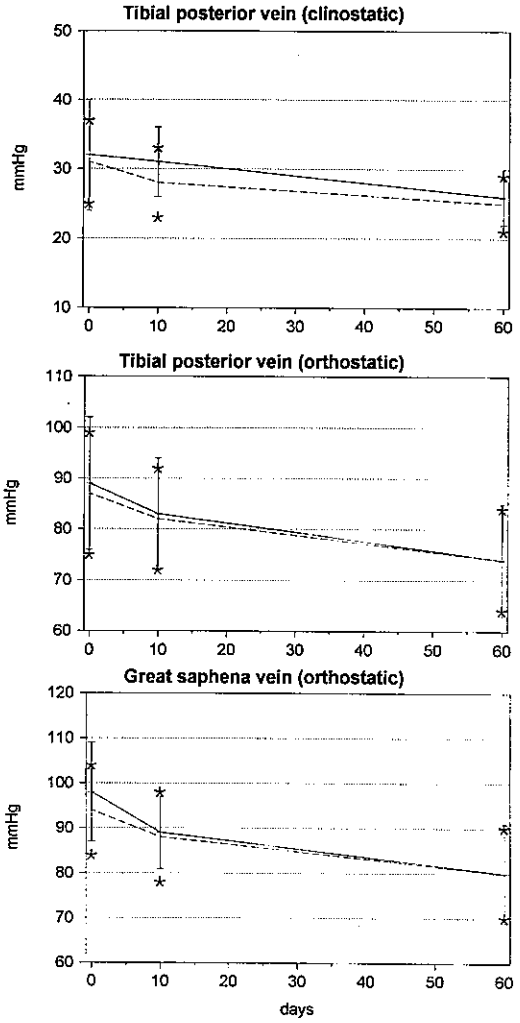

Figure 1. Behavior of CW Doppler venous pressures (mmHg) in Sulodexide-treated patients (dotted line; sd as *) and heparin-treated patients (continuous line; sd as ┬); P<0.001. (Multivariate test of significance for the effect of time on tested variable.)

The baseline laboratory values were comparable in the two groups (Table I). Both treatments and both dosage levels did not influence the PT. The PTT remained unchanged in Sulodexide-treated patients, while Ca-heparin administration yielded an increase, statistically significant vs baseline after ten days. Fibrinogen blood concentrations were, at the start of treatment, beyond the upper normal limit in both groups. A clear downward trend was detectable in both after ten days, with statistical significance of reductions versus the basal mean values. At the end of treatments, a further statistically significant decrease of fibrinogen blood levels was registered; only in Sulodexide-treated patients did such reduction bring fibrinogen values back within the normal range.

As to local tolerability, Sulodexide was, on the whole, far better tolerated than Ca-heparin. In fact, during Sulodexide IM administration, only 2 patients complained of slight pain at injection, which disappeared within fifteen minutes, and 1 patient complained, at the end of the oral administration period, of an episode of mild diarrhea, spontaneously resolved. On the other hand, during the SC administration of Ca-heparin, all patients complained—at least once during therapy and apparently without dependence on frequency of administration—of pain and/or burning sensation at the injection site, while 9 of 15 reported, after some injections, small hematomas (Ø <2 cm), which were reabsorbed within a few days. Compliance with treatment was without doubt better in the Sulodexide group.

Discussion

After a DVT episode, the most important structural alteration at the vein level is a major or minor valvular damage, which can have noticeable hemodynamic consequences. A correct antithrombotic treatment must therefore be started as soon as possible, in order to avoid the extension of fibrin formation and to reestablish the vascular canalization.[39] Among antithrombotic drugs, heparin is the most widely used;owing to its mechanism of action (binding to antithrombin III with consequent inactivation of a number of coagulation enzymes, thrombin, and factor Xa), heparin has a very strong anticoagulant effect[40,41] but also an elevated hemorrhage risk.[42] In the last few years, the search for antithrombotic drugs endowed with more and more reduced hemorrhage risk has been increasing, drawing physicians' attention to GAG fractions such as low-molecular-weight heparin and dermatan sulfate, which have shown very interesting capabilities.[43-46] Sulodexide contains both these GAG fractions, and it has been hypothesized that, owing to the simultaneous inhibition of thrombin by AT III and HC II,[47] this substance may be more effective than heparin in preventing thrombus formation and/or growth. Moreover, the antithrombotic effect of Sulodexide is achieved with less systemic anticoagulation than that associated with heparin.

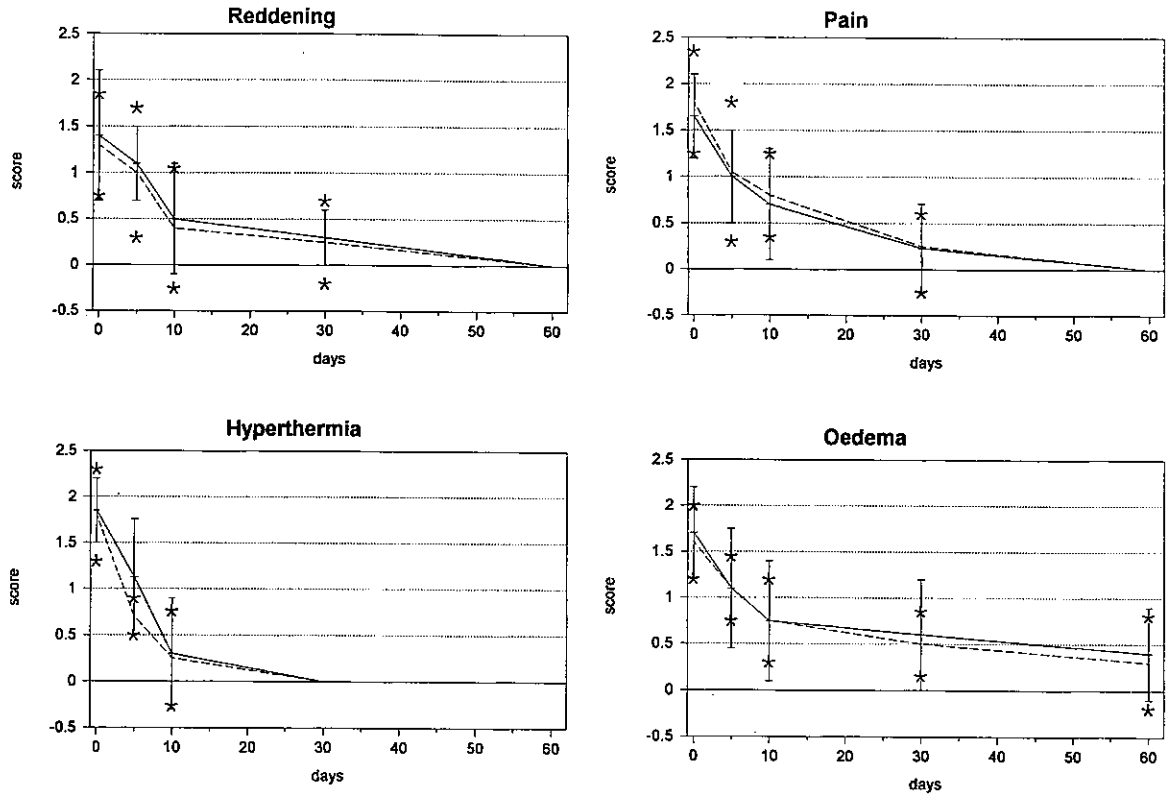

Figure 2. Mean scores of clinical symptoms in the Sulodexide group (dotted line; sd as *) and in the heparin-treated patients (continuous line; sd as ┬); P<0.001. (Multivariate test of significance for the effect of time on tested variable.)

Table I

Laboratory Data

	Baseline	10 days	60 days	P
Sulodexide				
Prothrombin time	96.2 ±3.3	95.4 ±3.4	95.8 ±2.9	ns
Partial thromboplastin time	35.4 ±5.6	36.2 ±7.2	35.6 ±6.4	ns
Fibrinogen	376.4 ±35.6	349.1 ±42.3*	331.6 ±45.8*	0.001
Calcium-Heparin				
Prothrombin time	97.0 ±3.1	94.5 ±4.2	94.5 ±4.0	ns
Partial thromboplastin time	35.2 ±5.1	42.1 ±7.9*	38.5 ±7.2	0.001
Fibrinogen	389.1 ±25.9	365.3 ±30.4*	360.0 ±35.6*	0.001

P level by the repeated measures ANOVA (univariate approach).
*P<0.05 vs baseline by the Student-Neuman-Keuls post-hoc test.

The results of our study provide evidence that the treatment of distal DVT by means of Sulodexide, administered mainly by the oral route, shares the same effectiveness as the classical subcutaneous treatment with Ca-heparin, in respect to the inhibition of upward thrombus accretion, improvement of venous pressures, elimination of the clinical signs of distal DVT, and fibrinogen-lowering activity. Our data also confirmed, through the statistically significant prolongation of PTT, the anticoagulant action exerted by Ca-heparin (not shared by Sulodexide, at least with the administration scheme adopted by us).

The better local tolerability of Sulodexide is to be ascribed, in our opinion, to the different administration routes employed; the prolonged use of the oral route is without doubt better accepted than the subcutaneous injections administered for sixty consecutive days. Strictly linked with this is also the patient's feeling toward the manifestation of hematomas: though not hazardous (they were all small and quickly disappeared without sequelae), this phenomenon can needlessly worry the patient, lowering compliance with treatment.

Conclusion

A medium-term treatment scheme with Sulodexide, performed mainly by the oral route, can be as effective as, and better tolerated than, a therapeutic course of Ca-heparin, performed exclusively by the SC route.

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