Use of sulodexide in patients with peripheral vascular disease

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Abstract: Sulodexide is a highly purified glycosaminoglycan containing a combination of heparan sulfate with affinity for antithrombin III and dermatan sulfate with affinity for heparin cofactor II. This antithrombotic and antithrombin activity is of great pharmacologic interest and makes sulodexide a suitable drug for the prophylaxis and treatment of arterial and venous peripheral diseases. In arterial pathology, changes in the Winsor Index, improvement in peripheral blood flow, and reduction in pain-free walking distance confirm that treatment with oral sulodexide is effective. Lipid components linked to the genesis of peripheral vascular processes, including triglycerides, total cholesterol, and low-density lipoprotein fractions, as well as plasma and blood viscosity, are reduced by the administration of sulodexide, whereas the high-density lipoprotein fraction increases. Sulodexide inhibits aggregation and adhesion of platelets at the level of the vascular wall, reduces plasma fibrinogen concentrations, reduces plasminogen activator inhibitor-1, and increases tissue plasminogen activator, as well as systemic fibrinolytic and thrombolytic activity, thereby demonstrating efficacy in the treatment of thromboembolic disease. There is no interaction between sulodexide and other drugs used as long-term treatment for peripheral vascular disease. It is well tolerated, and the adverse reactions described after oral administration are related mainly to transient gastrointestinal intolerance, ie, nausea, dyspepsia, and minor bowel symptoms. Sulodexide may become the treatment of choice when dealing with vascular diseases and their complications, as well as for the prevention of venous thromboembolic disease, being particularly indicated in elderly patients, due to its good tolerability and ease of management.

Keywords: sulodexide, peripheral vascular disease, safety, efficacy, venous thromboembolism

Introduction

Peripheral vascular disease includes both arterial (with the exception of cardiac and cerebral) and venous pathologies. The most common pathology is chronic arteriopathy of the lower limbs, which is a chronic and gradual process normally resulting from atherosclerotic injury. It becomes established mainly in the innermost layer of the arterial wall and causes arterial thrombosis as a final complication.¹ Venous vascular disease manifests as thrombosis, resulting from the synergistic interaction of endothelial damage, rheologic modification of blood flow, and hypercoagulability.²

The pharmaceutical arsenal for prophylaxis and treatment of atherothrombotic arterial pathology and venous thromboembolism includes several options, ie, hypolipidemic drugs,³ antiplatelet agents⁴ drugs with anticoagulant or antithrombotic
properties, such as warfarin or acenocoumarol, as well as nonfractionated heparin, low molecular weight heparin (LMWH),5,6 and dermatan sulfate.7

Sulodexide is a highly purified glycosaminoglycan (GAG) obtained from porcine digestive mucosa and is composed of a mixture of 80% heparan sulfate (an electrophoretically fast moving fraction with a low molecular weight of 7000 Da and affinity for antithrombin III) and 20% dermatan sulfate with a high molecular weight (25,000 Da) and affinity for the heparin II cofactor. This composition contributes to its antithrombotic and antithrombin action and a lower risk of hemorrhage.8–13 Sulodexide is therefore an ideal drug for the prophylaxis and treatment of arterial and venous peripheral vascular diseases.

Sulodexide has been marketed in Europe (Spain, Italy, and Eastern European countries), South America, and Asia. It is currently under development in the US as a treatment for diabetic nephropathy. The aim of this report is to summarize the biologic actions of sulodexide in peripheral vascular disease, as well as the results of studies evaluating the efficacy of sulodexide in patients affected by these pathologies.

**Pharmacokinetics of oral sulodexide**

**Absorption**

The pharmacokinetics of sulodexide in humans after oral administration of a single 50 mg or 100 mg dose in volunteers was evaluated in several studies by using radioactive isotopes, ie, C-14,14 I-131,11 I-125,15 and deuterium.16,17 After oral administration, sulodexide undergoes rapid and progressive intestinal absorption, with the presence of two peaks in plasma corresponding to both components (dermatan sulfate and heparan sulfate) and with concentrations of 0.2–1.0 mg/L at 1–10 hours after administration.14

After ingestion, sulfated GAGs are absorbed, undergoing significant degradation and loss of the sulfate groups, which in turn reduce the molecular weight of the drug. The desulfated derivates appear in the blood stream up to 3–4 hours after oral administration, accompanying the sulfated fractions for up to 24 hours, with no relevance from a pharmacodynamic point of view.17

Observation of the radioactive fraction linked to the unmodified drug indicates that the relative bioavailability of oral sulodexide is in the range of 40%–60%. Half-life after ingestion of a 50 mg dose is 18.7 ± 4.1 hours, and 25.8 ± 1.9 hours after a 100 mg dose.15

**Distribution**

Sulodexide undergoes rapid and progressive absorption, reaches high plasma concentrations, and is widely distributed, particularly in the monocellular endothelial layer, making it very interesting as far as blood clotting is concerned. Reduction in plasma concentration not only depends on rapid drug distribution, but also on binding with the endothelial cell receptors in both arteries and veins, due to the affinity of GAGs for this cellular layer.18–20 The long half-life of sulodexide may be due to the progressive liberation of products linked to these cells, and explains the long-term persistence of the drug in plasma. It is also possible that this process is influenced by metabolic degradation, reducing its affinity for cell receptors.17 Tissue uptake occurs via the extracellular matrix, as well as the renal and hepatic parenchyma.21

**Elimination**

Sulodexide is eliminated via the renal, bile, and fecal routes. Renal excretion is the main route, accounting for 55.3 ± 2.9% of drug excreted over 96 hours.11,15 A large part of the radioactivity excreted after 48 hours corresponds to degradation products as a result of intracellular biotransformation. Biliary excretion accounts for 23.5 ± 2.3% of the dose removed within 48 hours, and the remaining amount is eliminated by feces, accounting for 23.5 ± 2.8% at 48 hours.14

**Pharmacodynamics**

**Mechanism of action and pharmacologic effects**

From a pharmacologic point of view, sulodexide is very different from nonfractionated heparin due to its prolonged half-life and a systemic anticoagulant effect, which is less potent and therefore less likely to cause hemorrhage. Sulodexide, when administered orally exerts potent lipolytic activity,22 as well as activity related to proteoglycan synthesis by smooth muscle cells, associated with suppression of cell proliferation and inhibition of a significant part of atheromatous plaque development.16,23 At the same time, sulodexide inhibits migration of smooth muscle cells towards the innermost layer, as a result of the drug’s antithrombin and anti-platelet aggregation effect.24–26 The marked efficacy of sulodexide derives from its dual action of catalyzing the inhibition of thrombin by antithrombin III (ATIII) and by heparin cofactor II (HCII), with the added advantage of not increasing bleeding.27 Sulodexide possesses marked systemic fibrinolytic activity due to the liberation of tissue plasminogen activator (tPA), with marked functional and
antigenic reduction of plasminogen activator inhibitor-1 (PAI-1), and a reduction in plasma fibrinogen concentration, favoring the reduction of blood viscosity.

In short, oral administration of sulodexide has very effective antithrombotic and antithrombin activity, with efficacy and safety demonstrated in a wide range of vascular pathologies.

Rheology and sulodexide
The hemorrheologic mechanism is important in both peripheral arterial pathology and venous thromboembolic disease. Blood flow in patients can be determined by measuring blood and plasma viscosity, which are important parameters for measurement of atherosclerosis and thrombotic processes. Plasma viscosity depends on the plasma concentration of fibrinogen, although other proteins, such as immunoglobulins and lipoproteins, are able to increase viscosity. Increased viscosity leads to reduced blood flow, an increase in shearing forces, and alteration of the endothelial cells. Research on the hyper-viscosity phenomena in arterial vascular structures and their modification by sulodexide is particularly interesting. Many studies have found that sulodexide significantly reduces viscosity after intramuscular (IM) administration followed by long-term oral administration. Sulodexide administered exclusively via the oral route has also been shown to be effective in the treatment of disorders involving hyperviscosity. Oral administration of 50–100 mg doses results in a marked reduction of plasma viscosity, which can be observed as early as 1 week after the start of treatment. Some studies have found a significant reduction in global blood viscosity, whereas global viscosity has remained unchanged in other studies.

Lipids and oral sulodexide
Sulodexide was initially used primarily as a hypolipidemic drug due to its activity of liberating lipoprotein lipase after parenteral or oral administration. In a cholesterol-fed rabbit model, sulodexide significantly reduced plasma cholesterol levels and cholesterol accumulation in the rabbit abdominal aorta compared with controls. The disappearance of radiolabeled low-density lipoprotein (LDL) was enhanced after the addition of sulodexide in liver perfusates of healthy, lipemic, or hypertriglyceridemic rats. Sulodexide was shown to interact with very low-density lipoprotein (VLDL) by reducing lipoprotein uptake in the rabbit aorta and by increasing hepatic metabolism in normal and hypertriglyceridemic animals.

A similar response can be observed in the lipid profile of patients with peripheral vascular disease, as well as in those with diabetic vascular complications, in whom there is a marked reduction in triglycerides, an almost total response in the reduction of total cholesterol, and a variable response in the increase of high-density lipoprotein (HDL). Less significant is the reduction of the LDL fraction. In general, sulodexide’s influence on the lipid profile can be seen best after parenteral administration, but this is maintained during oral administration, even showing a trend towards improving the lipid profile further as treatment continues, and the lowest lipid concentrations being found at the end of oral treatment. Studies performed using only oral dosing demonstrated a significant reduction in triglyceride concentrations, with cholesterol levels remaining unchanged.

The determination of apolipoprotein levels, although less frequently studied, allows for the evaluation of situations of vascular risk and deterioration, and is an invaluable index for the study of atheromatous disease. In patients with peripheral vascular disease undergoing treatment with sulodexide (intramuscular + oral), an increase in apolipoprotein A-1 (Apo A-1) and a reduction in Apo lipoprotein B (Apo B) has been found, being particularly marked with oral administration, and more significant at the end of treatment. In a study of diabetic patients with vascular complications treated with sulodexide, an increase in Apo A-1 could be observed with no change in Apo B, while in another study of a comparable patient population, no modifications were observed.

Hemostasis and sulodexide
Until the 1970s, studies of the complex mechanism of hemostasis largely involved analysis of the extrinsic and intrinsic phases of blood coagulation, where plasma was the substrate. Few references were made to vascular permeability or to the vascular wall, the latter being considered to be merely a passive, inert hemostatic barrier. Since the 1970s, the study of hemostasis has focused primarily on the vascular wall, more specifically the vascular endothelium, where the main functions of hemostasis are centered, as well as the “in excess” pathologies of thrombosis and atherosclerosis, which are also currently receiving particular attention due to their immense socioeconomic importance.

Experimental studies have shown the effectiveness of heparan sulfate in both the prevention and treatment of venous thrombosis. In an early study, it was observed that heparan sulfate could inhibit venous thrombus formation as effectively as heparin, even at low doses. This is due to the fact that heparan sulfate can inhibit thrombus formation via
HCII, ie, not only via thrombin adherent to the fibrin of the thrombus, but also via free circulating thrombin.65,66

A comparative study of sulodexide and heparin in thrombus formation induced in the rabbit jugular vein demonstrated the efficacy of sulodexide in acceleration of thrombin inhibition by both ATIII and HCII. Sulodexide produced lower systemic anticoagulant activity, therefore reducing the probability of hemorrhagic complications.13

Sulodexide’s efficacy was also demonstrated in studies of thrombosis induced by ligation of the rat inferior vena cava.65,66 As in the induced thrombosis studies, a fibrinolytic effect was observed in rats and attributed to a reduction of plasma PAI-1 and increased tPA.64

Other investigators have assessed the activity of oral sulodexide in atherothrombotic disorders. In a pilot study of patients with hyperviscosity syndrome, a marked functional and antigenic reduction of PAI was observed, as well as an increase in tPA activity, both of which are endothelial components of the fibrinolytic system, with no change in plasma tPA concentration.24 In a double-blind, placebo-controlled, crossover study in patients with chronic peripheral vascular disease or recurrent venous thrombosis, a marked reduction was observed in serum viscosity (both P < 0.001) compared with placebo, probably due to an increase in tPA activity (P < 0.01), were observed after oral administration of sulodexide 100 mg/day for 30 days. No changes in global blood coagulation parameters, thrombin time (TT), partial thromboplastin time, or plasminogen concentrations were found. These data support the hypothesis that sulodexide accumulates in endothelial cells after oral administration. The same results were found in other randomized studies using 100 or 200 mg sulodexide.25,65

Interaction with other drugs
A number of concomitant cardiovascular diseases can affect middle-aged to elderly patients with peripheral vascular disease, resulting in polypharmacy in many cases. This has led to the study of the possible interactions of sulodexide with other drugs. No interference was found with the concomitant use of sulodexide and diuretics/antihypertensives, oral hypoglycemic drugs, gastric protectors, bronchodilators and expectorants, tranquilizers and anxiolytics, hepatic protectors, antibiotics/systemic disinfectants, nitroderivatives, insulin, and LMWH.66–68 To summarize, oral administration of sulodexide in cardiovascular disease, metabolic disease, and in the prevention and treatment of thromboembolic disease, does not interfere with the pharmacologic action of other commonly used treatments.

Efficacy in peripheral vascular disease
Peripheral arteriopathy
Peripheral, obstructive, chronic arteriopathy is a common disorder and is caused by low perfusion pressure causing pain at rest and trophic changes in the lower limbs. Pain is intense, particularly at night, and leads to psychologic and clinical deterioration in many patients. The pharmacologic arsenal comprises drugs directed not towards resolving obstructive arteriopathy, but towards improving circulation, viscosity, and arterial blood flow to relieve pain and trophic changes.

A large number of clinical studies have been performed with sulodexide in this setting, some of which were double-blind,35–39,49,50,69–72 most were placebo-controlled, and some followed an open design.41,73–78 All studies included patients with Leriche-Fontaine stages I–III disease, ranging from no clinical symptoms to intermittent claudication and significant symptoms. Depending on the study, patients initially received IM sulodexide (generally 60 mg) for 20 days, followed by oral administration (60 mg/day) for 40 days to 6 months.

Treatment with sulodexide significantly improved clinical symptoms, as well as objective and functional signs in these studies. Improved tissue perfusion at the muscle level was indicated by better walking distance on treadmill testing. This improvement in muscle perfusion is attributable to the reduction of plasma, total blood, and serum viscosity (the latter being less marked), and is the main objective of treatment with sulodexide. Results using the Winsor Index, Doppler, and plethysmography confirm that oral treatment is capable of maintaining the benefit achieved after initial parenteral sulodexide treatment. The continuation of oral sulodexide is important from a biologic perspective, because oral administration stabilizes, prolongs, and improves the effects achieved by the parenteral route.

In other double-blind, placebo-controlled studies, sulodexide was administered only by the oral route to patients with Leriche-Fontaine stages I–II peripheral vascular disease23,45,66 or cerebrovascular disease.22 The doses administered varied from 50–100 mg/day for 30–90 days. The Winsor Index and treadmill test performance improved significantly (both P < 0.001) compared with placebo, probably due to improved local perfusion.66

A marked reduction was observed in serum viscosity (P < 0.001), fibrinogen levels (P < 0.05),23,45 and in vitro platelet aggregation (P < 0.05).22 A similar effect was observed on the lipid profile, with a significant reduction in triglycerides (P < 0.01), and a significant increase in HDL.
(P < 0.05).\textsuperscript{22,23} Decreased concentrations of fibrinogen, plasma viscosity, total blood, and platelet aggregability were all considered to be responsible for improved blood flow and, subsequently, improved clinical symptoms.

In summary, the observed modifications in the Winsor Index, improved peripheral blood flow, and decreased claudication symptoms indicate that treatment with oral sulodexide is effective in eliminating or reducing functional damage and clinical symptoms caused by chronic peripheral arteriopathy, when still amenable to medical therapy. Similar findings have been reported in diabetic patients with peripheral vascular disease.\textsuperscript{79} Importantly, the reduction of plasma fibrinogen by sulodexide has been observed not only in clinical studies of parenteral and oral dosing, but in studies using only oral sulodexide administration.

Arteriosclerosis associated with metabolic disorders
This section reviews the studies performed in patients with peripheral vascular disease associated with metabolic disorders, in particular diabetes and hyperlipidemia. Three double-blind, placebo-controlled studies are reviewed.\textsuperscript{80–82} The dosage was fairly uniform, with the parenteral phase consisting of 30–60 mg/day administered via the IM route for 10–30 days, followed by 60 mg/day orally for up to 90 days. In the first study, the results demonstrated a reduction in lipid parameters for both diabetics and nondiabetics, and a further progressive reduction during oral administration.\textsuperscript{80}

The next study was done in patients with peripheral arteriosclerosis and Leriche-Fontaine Stage II vasculopathy, having claudication and other symptoms requiring chronic therapy (excluding insulin-dependent diabetes and hyperlipidemia). A significant reduction of triglycerides (P < 0.05) and an increase in HDL (P < 0.05) was observed in sulodexide-treated patients compared with placebo. Likewise, peripheral circulatory assessment improved significantly on oscilometry (P < 0.01) and plethysmography (P ≤ 0.05).\textsuperscript{81} Another study in patients with generalized atherosclerosis, diabetes, and altered lipid metabolism showed a marked reduction in triglycerides (P < 0.001) and cholesterol (P < 0.05), as well as increased HDL (P < 0.01), with a reduction in blood (P < 0.05), plasma (P < 0.01), and serum (P < 0.01) viscosity in the sulodexide group, mainly during the oral administration period.\textsuperscript{82}

Five open, uncontrolled studies,\textsuperscript{40,83–86} in patients with generalized atherosclerosis, cerebral vasculopathy, chronic arterial insufficiency, and/or heart disease demonstrated similar results. A marked reduction in triglycerides (P < 0.001) and cholesterol (P < 0.05) were observed in patients with dyslipidemia Type IV, the reduction being less marked in those with Type IIb dyslipidemia. In general, significant improvement was seen for intermittent claudication (P < 0.001) and night pain and cramps (P < 0.001). The same effect was observed in patients with heart disease and anginal symptoms, in whom no recurrences of symptoms were documented. With regard to cerebrovascular symptoms, a mid to high percentage of patients demonstrated a favorable outcome at the end of oral treatment, being very effective in the prevention of recurrent transient ischemic attacks.

In summary, in dyslipidemic patients with a profile of atherosclerosis affecting different organs, administration of sulodexide normalized the relevant atherosclerotic parameters and produced favorable clinical outcomes for patients.

Vascular complications of diabetes
It is well known that diabetes in adults is an important risk factor for atherosclerosis, progressing to arteriopathy of the lower limbs and often requiring amputation. Prevention of thromboembolic complications is therefore essential and has led to the study of the efficacy of sulodexide in diabetic patients with atherosclerosis.

The clinical and laboratory findings of various studies carried out in diabetic patients with vascular complications\textsuperscript{51,52,73,87–90} have been particularly interesting. In these studies, sulodexide was administered as 60 mg/day intramuscularly for 20 days followed by 60 mg/day orally for 70 days. In a double-blind study of diabetic patients with Leriche-Fontaine grades II–III peripheral arteriopathy,\textsuperscript{51} a reduction in total lipids was observed (P < 0.02) at the end of treatment, corresponding to a reduction in total cholesterol (P < 0.05) and triglycerides (P < 0.005). Additionally, an increase in HDL was achieved (P < 0.03), as well as in Apo A (P < 0.02). No changes in Apo B or fibrinogen were observed. The change in lipid profile correlated with improvement in symptoms of intermittent claudication.

In another study of patients with vascular complications,\textsuperscript{87} there was a progressive reduction in total cholesterol (P < 0.001), an increase in HDL (P < 0.05), and a significant reduction of plasma fibrinogen (P < 0.001). These findings were again accompanied by improvement in vascular symptoms, including those of intermittent claudication.
Patients with dyslipidemia and severe atherosclerotic symptoms have been investigated, and found to show improvement in cerebrovascular, coronary, and peripheral arterial symptoms. Cholesterol ($P < 0.001$) and triglycerides ($P < 0.05$) were significantly reduced, which explains the clinical benefit experienced by the majority of patients.

Treatment with sulodexide was also evaluated in an open, randomized study of patients with types 1 and 2 diabetes mellitus or impaired glucose intolerance, accompanied by arterial vasculopathy of the lower limbs, retinopathy, and coronary artery disease. Changes in plasma parameters were assessed, as well as clinical outcomes. The majority of patients (48%) showed clinical and subjective improvement accompanied by a reduction in platelet adhesion ($P < 0.01$) and fibrinogen levels ($P < 0.05$). Triglyceride, total cholesterol, HDL, total lipid, and Apo A and B levels did not show any significant reductions. However, the reduction of platelet adhesion found at the end of treatment is noteworthy, being particularly interesting for the clinical evolution of patients with atherosclerotic injuries.

Finally, three open studies, including diabetic patients with vascular complications were reviewed. A reduction in plasma triglycerides ($P < 0.05$) and total cholesterol ($P < 0.05$) were observed in all patients. A significant reduction in fibrinogen ($P < 0.05$) was seen in one of the studies compared with a slight reduction at the end of treatment in other study. In all groups, improvement in intermittent claudication symptoms was observed ($P < 0.001$, $P < 0.05$, and $P < 0.01$) and was seen mainly during oral treatment.

**Prophylaxis and treatment of venous thromboembolic disease**

The efficacy of sulodexide in the prevention and treatment of venous thromboembolic disease lies in its bioavailability after oral administration and in its affinity for endothelial and subendothelial cellular elements. Six studies were reviewed in which doses of 50–100 mg/day were administered for up to 24 months. Patients with deep vein thrombosis (DVT), varicose syndrome, and recurrent thrombosis were studied in a double-blind, placebo-controlled crossover study. During the administration phase, a very significant ($P < 0.001$) PAI antigen reduction was observed compared with baseline, and no change on placebo. The concentration of fibrinogen in plasma was slowly reduced during treatment with sulodexide, and was statistically significant at the end of treatment ($P < 0.001$), again not observed with placebo. Fibrinolytic activity studied using the fibrin plaque technique also showed a significant increase ($P < 0.01$).

These results are consistent with those of other clinical trials, whereby prophylactic activity was related to a significant reduction in plasma fibrinogen ($P < 0.05$) and PAI ($P < 0.001$), with no change in antithrombin and TT, indicating a systemic anticoagulant effect. These results justify the use of sulodexide at the recommended doses in patients with venous disorders and at risk of thrombotic complications.

In a multicenter, randomized, double-blind, double-masked trial, patients with chronic venous insufficiency secondary to varicose syndrome or to a thrombotic episode confirmed by Doppler were allocated to receive 50–100 mg/day of sulodexide for 60 days. The results demonstrate a significant improvement in venous pressure, assessed in the saphenous and tibial veins, with significant clinical improvement in all groups ($P < 0.001$) at the end of treatment, which can be attributed to the effect of sulodexide on thrombotic factors, ie, tPA, fibrinogen, and plasma viscosity, which was more rapid in patients receiving doses of 100 mg/day.

The incidence of long-term recurrent thrombosis was evaluated in a multicenter study of patients with confirmed DVT. The patients were treated during the acute phase with the normal dosing schedule of heparin plus oral anticoagulation for 6 months. At the end of this period the patients were randomized to receive sulodexide 50 mg/day for 24 months or to a control group without medication. At 6 and 12 months, the incidence of recurrent venous thrombosis was significantly lower in the treated group ($P < 0.05$). At 24 months, the overall incidence of recurrent thrombosis was 17.9% in the control group and 7.4% in the treated group ($P < 0.05$). Oral administration of sulodexide prevented 40%–60% of recurrent thromboses over a 2-year period, and confirmed the efficacy of sulodexide as prophylaxis for thromboembolic disease.

Sulodexide was also compared with acenocoumarol as secondary prophylaxis for DVT in a controlled, open, parallel-group pilot study. Patients in the sulodexide group received 60 mg/day for 3 months and the other group received acenocoumarol adjusted according to INR. There were no differences in clinical outcome or in the number of thrombotic complications. No hemorrhagic complications were observed in the sulodexide group, whereas 1 major hemorrhage and 9 episodes of minor hemorrhage occurred in the acenocoumarol group ($P = 0.014$). These results suggest sulodexide may be...
used as an alternative to acenocoumarol in this patient population.

Prophylaxis of venous thromboembolic complications is particularly important in the immobile elderly. A study was performed in elderly patients with hemiparesis at high risk of thromboembolic complications and suffering from a variety of concomitant conditions, including ischemic heart disease (7%), diabetes (30%), and dyslipidemia (20%). Treatment consisted of sulodexide 60 mg intravenously twice daily for 1 month, followed by 50 mg/day orally for a further month. No venous, cerebral, or cardiac thromboembolic episodes were detected during the 2 months of treatment, in spite of a mean age of 71.6 (61–81) years, with immobility and comorbidity.

The efficacy of sulodexide has also been studied in patients affected by venous ulcers of the lower limbs. Chronic venous stasis produces deterioration of endothelial cells, alteration in the microcirculation, including inflammation, and, with time, the development of ulcers resistant to treatment. In a randomized, placebo-controlled study of patients affected by venous ulcers of the lower limbs, sulodexide 60 mg/day IM was administered for 20 days, followed by 100 mg/day orally for 70 days. Patients treated with sulodexide showed complete resolution of venous ulcers after both 2 and 3 months of treatment ($P = 0.018$ and $P = 0.004$, respectively).

**Prophylaxis of trauma-related venous thromboembolic disease**

In traumatology there is evidence that dermatan sulfate has a prophylactic effect, due to the fact that it catalyzes thrombin inhibition by HCl.$^{96}$ Two clinical studies were reviewed to assess the efficacy of sulodexide as prophylaxis in patients undergoing arthroplasty of the hip or knee. The first was a prospective controlled study in which postsurgical treatment was started in hospital with the administration of LMWH, followed by sulodexide 60 mg/day for 30 days. Echo Doppler was performed on days 15 and 30 of sulodexide treatment. The results showed significant ($P < 0.0001$) efficacy in thromboembolic prevention in patients who completed their prescribed course of sulodexide treatment. In another open study in patients undergoing arthroplasty of the knee, thromboembolism prophylaxis was started after discharge from hospital. All patients were treated with LMWH during their postoperative stay and afterwards received 60 mg/day sulodexide for 30 days. At the end of the study, 95.8% of patients were free of thrombotic complications; only four cases were observed, two of which were asymptomatic. In summary, sulodexide is capable of significantly reducing thromboembolic complications in patients who have undergone arthroplasty of the hip, and is an ideal choice for outpatient treatment.

**Economic considerations**

Some research has been performed assessing the cost of treatment with sulodexide, mainly in DVT prophylaxis. In a previously mentioned study, patients with DVT were treated with LMWH followed by oral anticoagulation for 6 months and were subsequently allocated to receive either 50 mg/day of sulodexide for 2 years or follow-up with no other pharmacologic support. The average cost of treating one DVT episode was estimated at €23,000, which was equivalent to the annual cost of treating 53 patients with sulodexide. According to this study, sulodexide prevented 7–8 recurrent DVT episodes per 100 patients per year. The treatment of 53 patients with sulodexide therefore prevents 4–5 recurrent thromboses, with corresponding cost savings.

In a pilot study of secondary DVT prophylaxis, an analysis was performed to analyze the costs associated with treatment using sulodexide or acenocoumarol. The estimated costs were based on the doses used in the clinical trials of sulodexide 60 mg/day or acenocoumarol 2 g/day and 3 months of treatment. The analysis considered the necessary INR adjustments, follow-up visits, and corresponding laboratory tests in accordance with normal clinical practice. It was also assumed that neither additional visits nor complementary tests were necessary with sulodexide. The analysis demonstrated a cost-saving per patient of 500% with sulodexide compared with acenocoumarol during the study period (€484 at the time of the analysis). The sensitivity analysis was strongly in favor of sulodexide. It is important to note that only data on efficacy were analyzed. Indirect costs, such as loss of productivity resulting from visits associated with acenocoumarol, were not considered.

In both cases, cost-analysis in favor of sulodexide needs to be considered in the context of the number of target patients treated in a reference hospital or outpatient vascular departments, which would provide great savings to the health services.

**Safety profile**

Oral administration of sulodexide is extremely well tolerated, to the extent that no adverse events were reported in some of the studies reviewed, with a very low incidence in others. The adverse effects consist mainly of transient gastrointestinal disturbances appearing at the start of treatment, and include diarrhea, epigastralgia, dyspepsia, heartburn,
dizziness, and other minor digestive problems. These events were assessed to be of mild to moderate intensity, and generally did not require interruption of treatment. Allergic reactions, such as skin rash, have also been reported but are very rare.

Of particular interest is a randomized multicenter study in which 2016 post–myocardial infarction patients received sulodexide 100 mg daily for 11 months. The adverse events recorded were 7 cases of nausea and vomiting, 5 cases of epigastralgia, and 4 skin reactions. None of these cases required interruption of treatment.

In summary, the adverse effects reported in the clinical studies with oral sulodexide largely relate to the gastrointestinal system, are short-lasting, of low incidence, and resulting in an excellent safety profile.

Conclusion
Considerable clinical experience has been gained with sulodexide since it entered the marketplace. Its pharmacologic action on the essential mechanisms causing atherothrombotic disease, on lipid metabolism, the blood clotting mechanism at the vascular wall level, and blood rheology dynamics positions sulodexide as a drug which is effective in the treatment of peripheral arterial diseases and their complications, as well as in the prevention of venous thromboembolic disease. Sulodexide is a comparatively safe drug, without the well-known hemorrhagic complications associated with some other compounds (eg, coumarin derivatives and heparin). The adverse effects described after oral administration in the clinical trials were short-lasting and consisted mainly of gastrointestinal disturbances, their incidence being of low significance.

Oral administration of sulodexide does not demonstrate any pharmacologic interactions requiring suspension or dosage modification in patients being treated for vascular diseases and/or metabolic disorders, or in the prophylaxis and treatment of venous thromboembolic disease. Sulodexide does not require monitoring for dose adjustment, so it is particularly suitable for middle-aged to elderly patients.

Disclosures
PC and MG are employees of Tedec-Meiji Farma S.A., Madrid, Spain. They do not own stocks or options in the company. The other authors declare no conflicts.

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