

Sulodexide: A Renewed Interest in This Glycosaminoglycan

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ABSTRACT

Glycosaminoglycans (GAGs) are the most abundant group of heteropolysaccharides found in the body. These long unbranched molecules contain a repeating disaccharide unit. GAGs are located primarily in the extracellular matrix or on the surface of cells. These molecules serve as lubricants in the joints while at the same time providing structural rigidity to cells. Sulodexide is a highly purified glycosaminoglycan composed of a fast mobility heparin fraction as well as dermatan sulfate. Sulodexide differs from other glycosaminoglycans, like heparin, by having a longer half-life and a reduced effect on systemic clotting and bleeding. In addition, sulodexide demonstrates a lipolytic activity that is increased in comparison to heparin. Oral administration of sulodexide results in the release of tissue plasminogen activator and an increase in fibrinolytic activities. An increasing body of research has demonstrated the safety and efficacy of sulodexide in a wide range of vascular pathologies.

INTRODUCTION

Glycosaminoglycans (GAGs) are a naturally occurring group of compounds that have found clinical use in the prevention of thrombotic events. This group of molecules makes up the most abundant group of heteropolysaccharides in the body. GAGs are negatively charged molecules characterized by long, unbranched polysaccharide chains that contain a repeating disaccharide unit. The disaccharide units contain either of two modified sugars, N-acetylgalactosamine or N-acetylglucosamine, and a uronic acid such as glucuronate or iduronate (26,43,56).

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Clinical usage of GAGs for the treatment of thrombotic diseases is not without risks however. For example, heparin has been shown to have various side effects including heparin-induced thrombocytopenia. Therefore, efforts to develop alternative therapies have resulted in the introduction of low molecular weight heparins and small molecules targeted to selective sites in the coagulation cascade.

One of these alternatives, sulodexide, is a highly purified GAG that is composed of two distinct fractions. The mixture of GAGs is obtained from the porcine intestinal mucosa by a patented process (37). The chemical composition of sulodexide is defined as 80% fast mobility heparin (FMH) and 20% dermatan sulfate (DS). FMH fraction is described based on its electrophoretic mobility. The FMH component is present in commercial unfractionated heparin together with a slower electrophoretic mobility fraction. FMH and DS are further characterized by having a lower degree of sulfation and lower anticoagulant activity than unfractionated heparin.

The low molecular weight of both sulodexide fractions allows for extensive oral absorption compared to heparin. In rats, pharmacodynamic effects were observed within three hours of oral administration and a cellular distribution of fluorescent material was observed in the kidney, liver and endothelium of veins and arteries (21,67). The pharmacokinetics in man has been evaluated using deuterium-labeled sulodexide (12). A single 100 mg dose of deuterated sulodexide was administered to healthy volunteers intravenously or orally. After intravenous dosage the elimination half-life of the FMH was 1.0 h and DS was 1.6 h. Peak plasma levels were 20 mg/L and 8 mg/L, respectively. Oral administration of sulodexide resulted in peak plasma levels of both compounds ranging from 0.2–1.0 mg/L approximately 1–10 h after dosing.

Sulodexide (Vessel™), a product developed by Alfa Wassermann, has been marketed for more than twenty years in Italy, Spain, Eastern Europe, South America, and Asia for the treatment of various cardiovascular conditions. Currently, Keryx Biopharmaceuticals is developing sulodexide (Sulonex™) as a treatment for diabetic nephropathy in North America. Sulonex™ is currently in Phase III and Phase IV clinical trials under a Special Protocol Assessment with the United States Food and Drug Administration.

PHARMACOLOGY AND CLINICAL STUDIES

Anticoagulant and Antithrombotic Activity

Survivors of acute myocardial infarction are at high risk for the recurrence of thrombosis and sudden cardiac arrest is a major health problem, causing about 330,000 deaths each year among U.S. adults either before reaching a hospital or in an emergency room. Major research efforts in academic settings and pharmaceutical companies have focused on investigating various antithrombotic agents for the secondary prevention of acute coronary syndrome. The goal is to develop agents that can be administered by the oral route with minimal potential for inducing marked alterations in hemostasis.

GAGs exert an antithrombotic action by interacting with naturally occurring serine protease inhibitors such as antithrombin III (ATIII) and heparin cofactor II (HCII) (3,17). As a result of these interactions, the inhibition of activated serine proteases in the coagulation cascade by ATIII and HCII is accelerated more than 1000 fold (38,42,69). Thrombin is the central serine protease of the coagulation system as it promotes cleavage of fibrino-

gen into fibrin, which then polymerizes leading to the formation of occlusive arterial or venous thrombi (58,59) or thromboemboli originating from the left atrium in patients with atrial fibrillation. Thrombin can also exert positive feedback on itself by activating factor VIII and factor V (30). The inhibition of thrombin formation and its proteolytic action are the primary mechanisms by which GAGs exert their anticoagulant and antithrombotic effects (57,71).

Thrombin is the essential serine protease of the coagulation cascade that promotes the deposition of thrombi by cleaving fibrinogen to fibrin, which then polymerizes, under the influence of thrombin-induced activation of FXIII thereby forming a stable occlusive intravascular thrombus. Thrombin also exerts a positive feedback on its own generation by activating FVIII and FV.

The FMH and DS fractions of sulodexide accelerate the inhibition of thrombin by their simultaneous interactions with ATIII and HCII, respectively (10,52). As a result, they directly inhibit thrombin and also thrombin generation by inhibiting the feedback activation of prothrombin (30). Sulodexide prolongs the thrombin clotting time and the activated partial thromboplastin time (aPTT).

The heparin-induced activation of ATIII retards thrombus growth and thrombus formation along with the induction of a hypocoagulable state. A major limitation to the efficacy of heparin is its inability to inhibit the proteolytic activity of thrombin that is bound to fibrin or incorporated into the thrombus. In contrast, the inhibition of fibrin-bound thrombin by the HCII/DS complex is not impaired (50). In an *in vivo* study (8), it was determined that pretreatment with heparin, 10 antithrombin units per 1 kg (10 U/kg), inhibited clot formation to the same extent as 5 U/kg of sulodexide. Thus, sulodexide administered in half the antithrombin dose of heparin was equally as effective in preventing thrombus formation. The results are consistent with the hypothesis that thrombin inhibition by the simultaneous activation of ATIII and HCII has a greater efficacy than heparin. The synergistic effect is evident by the observation that a lower dose of sulodexide achieved an equivalent antithrombotic effect as a higher dose of heparin in preventing thrombosis (7,8,18). The greater efficacy of sulodexide derives from its dual action of catalyzing the inhibition of thrombin by ATIII and by HCII with the added advantage of a limited potential for inducing increased bleeding. The latter may be related to the absence of an influence on aPTT as indicated by the lack of interference of sulodexide on the intrinsic coagulation pathway (53). The different sites in the coagulation cascade where sulodexide exerts anticoagulant effects are illustrated in a review by Davie and Kulman (22).

In an acute experimental model where the thrombus formation was induced in the carotid arteries of rats by electrical stimulation, sulodexide significantly prolonged the time to vessel occlusion (maximum fall in temperature) in a dose-dependent manner after intravenous bolus administration, with an efficacy similar to that of heparin or aspirin (2). The study results also demonstrated the ability of sulodexide to prevent *ex vivo* platelet aggregation in response to thrombin, but not to arachidonic acid. The ability to preserve partial platelet reactivity might account for the fact that sulodexide exhibits a limited potential to induce uncontrolled bleeding.

Using a chronic rat model of arterial thrombosis, sulodexide was compared to heparin to analyze the ratios of the antithrombotic/bleeding effects of the respective anticoagulants (40). At doses that were equally as effective at preventing arterial thrombosis, hepa-

rin-bleeding time was 2 times longer than baseline, while sulodexide produced a 25% prolongation in bleeding time.

Clinical trials have demonstrated the beneficial effects of sulodexide in the treatment of deep vein thrombosis. Errichi et al. reported that after 6, 12, and 24 months of oral sulodexide treatment (50 mg daily) the recurrence of deep vein thrombosis was significantly attenuated ($p < 0.05$) in high-risk subjects (27). A more recent trial compared sulodexide with acenocoumarol in the secondary prophylaxis of patients with deep vein thrombosis (14). In this study a fixed dose of sulodexide (30 mg, four doses per day) was compared with adjusted doses (international normalized ratio) of acenocoumarol. There were no differences in either clinical evolution of the disease or the number of venous recurrences over the course of the treatment period between groups. In the group treated with sulodexide there were no hemorrhagic complications. In the acenocoumarol group, however, one major hemorrhage (requiring discontinuation of the anticoagulant) and nine minor hemorrhages (not requiring discontinuation of the anticoagulant) were recorded. The difference in adverse events was statistically significant ($p = 0.014$). These results coupled with the high cost of acenocoumarol monitoring reinforce the benefits of sulodexide in the management of certain thrombotic diseases.

Sulodexide has also been found effective in the treatment of venous leg ulcers (15). Chronic venous stasis of the lower extremities results in endothelial damage causing the formation of thrombi. Impairment of the microcirculation of the skin induces chronic inflammation and ulceration. In this study 235 patients undergoing local treatment of leg ulcers were randomized to either sulodexide (60 mg daily i.m. for 20 days, followed by 100 mg/day p.o. for 70 days) or placebo treatment groups. The proportion of patients with complete ulcer healing was higher in the sulodexide group at 2 months ($p = 0.018$) and 3 months. Additionally, ulcer surface area and fibrinogen levels were significantly reduced in the sulodexide group compared to placebo ($p = 0.004$ and 0.006 , respectively).

Similarly, the beneficial effects of sulodexide have been seen in the treatment of intermittent claudication. Intermittent claudication is defined as painful cramping in the legs that is present during exercise or walking and occurs as a result of decreased blood flow to the legs. This phenomenon occurs in individuals with peripheral arterial obstructive disease. In a randomized, double-blind, placebo controlled trial (16), sulodexide (60 mg daily i.m. for 20 days, followed by 100 mg/day p.o. for 6 months) successfully doubled the pain free walking distance in 23.8% of patients while only 9.1% achieved a doubling in the placebo group ($p = 0.001$). The pain-free walking distance increased by 83.2 ± 8.6 m (mean \pm standard error) with sulodexide and 36.7 ± 6.2 m with placebo.

In addition to the antithrombotic effects of sulodexide, administration of the compound to animals with preexisting thrombi demonstrates a dose dependent reduction in thrombus size (4). It was suggested that this effect could be attributed to the activation of tissue plasminogenic activator and/or the inhibition of plasminogenic activator 1 (12,20).

Prevention of Reperfusion Injury

The restoration of myocardial blood flow to a previously ischemic region is associated with a complex series of events leading to tissue injury greater than that which is attributed to the original period of flow deprivation, an event referred to as "reperfusion injury."

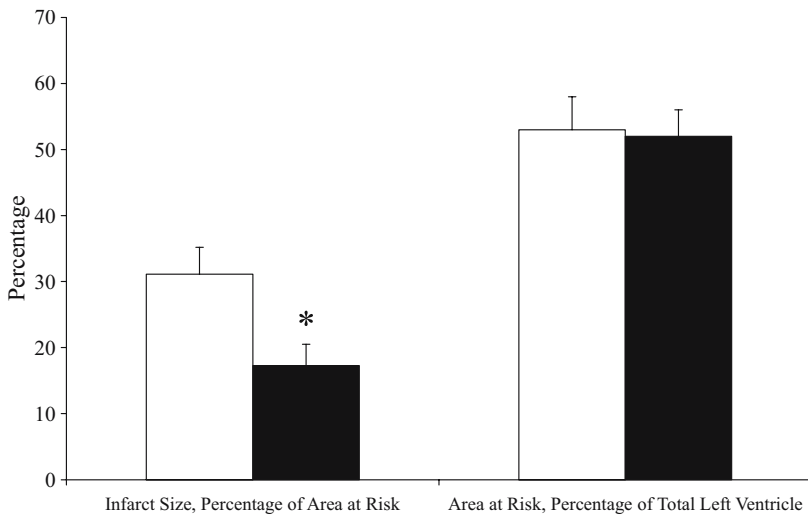


FIG. 1. Effects of sulodexide on myocardial infarct size after 30 min of left anterior descending coronary artery occlusion and 4 h of reperfusion compared with saline vehicle. Infarct size after reperfusion is expressed as a percentage of the area at risk. The areas at risk were similar between groups. This indicates that the degree of the insult was similar. Data are presented as means \pm S.E.M.; vehicle group, $n = 10$ (white bars); sulodexide group, $n = 10$ (black bars); * $p < 0.05$ vs. vehicle. Figure was adapted from ref. 48 with permission of the American Society for Pharmacology and Experimental Therapeutics.

The complement system is a component of the innate immune system consisting of a group of proteins circulating in the blood. The components of the complement system act together to recognize and destroy foreign pathogens. Activation of the complement system, however, can also have adverse effects on host tissues. In the setting of myocardial reperfusion injury, the complement system represents an integral mechanism through which the ischemic tissue undergoes injury leading to irreversible tissue injury and cell death (45,61). Previous studies provided evidence for the role of complement by demonstrating the deposition of the terminal complement complex, or the membrane attack complex (MAC), in irreversibly injured myocardial tissue (68). The authors offered the suggestion that the initial period of ischemia may cause loss of the ability of the heart muscle cells to regulate complement turnover at the membrane level. The resulting deposition of C5b-9 (membrane attack complex) on the cell membranes may contribute to functional disturbance and irreversible damage of myocardial cells during the infarction process. It is hypothesized that pharmacological inhibition of complement activation would be beneficial in reducing tissue injury associated with ischemia and reperfusion.

Various GAGs have been reported by our laboratory to be of benefit to the ischemic myocardium by preserving contractile function and reducing tissue injury (6,29,35,46,70). In addition, selective GAGs are known to possess anti-complement activity in addition to their classical roles as anticoagulants. Recently we reported that sulodexide effectively reduced myocardial infarct size after ischemia and reperfusion in the rabbit heart when administered periodically throughout the four hour reperfusion period (48) (Fig. 1). Sulodexide was demonstrated to inhibit complement activation, possibly through the inhibition of C-reactive protein (CRP), resulting in a reduction in the extent of myocardial injury as-

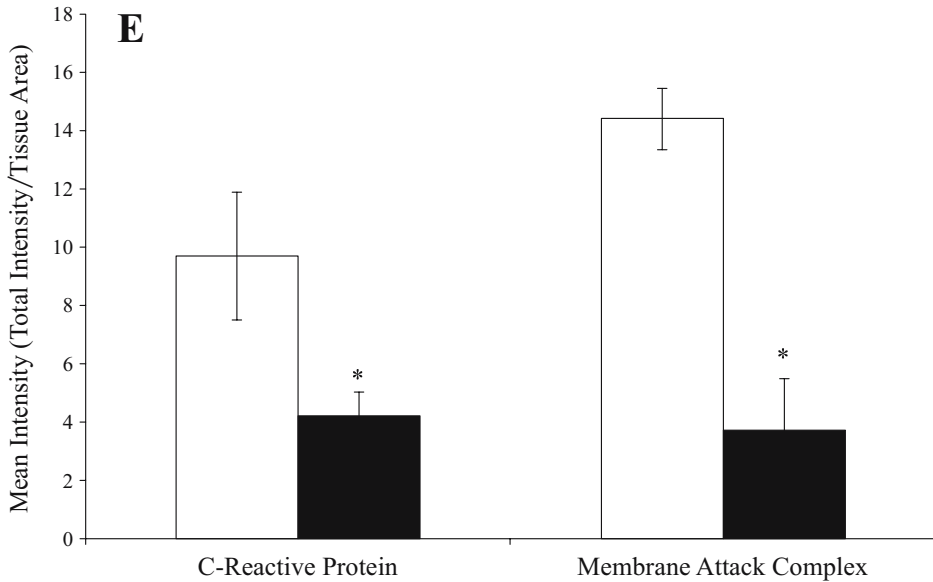
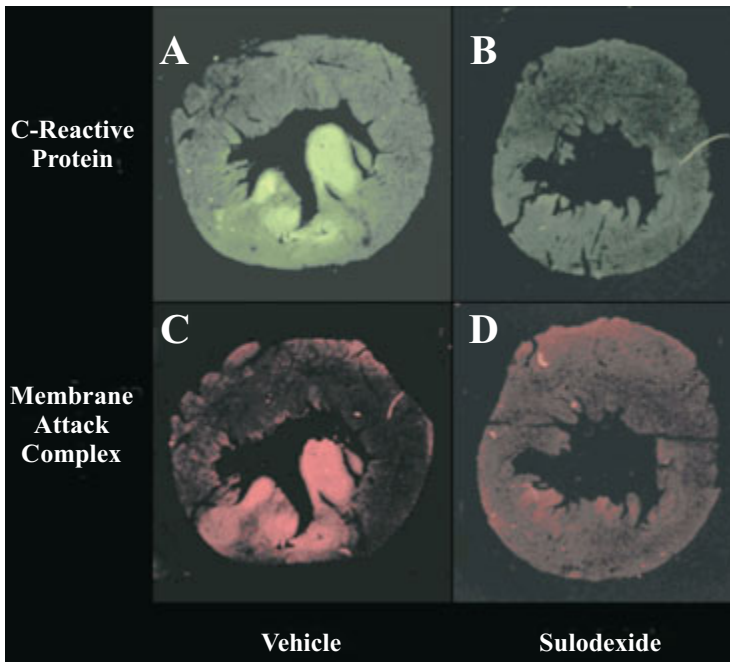


FIG. 2. Representative fluorescent images of a heart from a control animal (A and C) and an animal treated with sulodexide (B and D) after 30 min of ischemia and 4 h of reperfusion. Prepared heart sections were immunofluorescently stained for C-reactive protein (CRP) and for the membrane attack complex (MAC). Each section was quantified using a fluorescent stereoscope with the accompanying software. In the vehicle-treated animal, staining for CRP (A) and MAC (C) is present in areas of infarction. In sulodexide-treated hearts, little or no staining for CRP (B) or MAC (D) can be observed in areas of infarction. (E), graph illustrating the comparison of mean fluorescence intensity per heart section. Values are presented as mean \pm S.E.M.; vehicle group, $n = 3$ (white bars); sulodexide group, $n = 3$ (black bars); * $p < 0.05$ vs. vehicle control. Figure was adapted from ref. 48 with permission of the American Society for Pharmacology and Experimental Therapeutics.

sociated with ischemia/reperfusion (Fig. 2). The data indicate that there is a separation between the anticoagulant and anti-complement effects of sulodexide by utilizing a dose of the compound that was found previously to have little or no effect on coagulation (37) while retaining the ability to protect the ischemic myocardium.

Heparin and related non-anticoagulant glycosaminoglycans are reported to reduce the extent of myocardial injury. This effect has been attributed to an anti-inflammatory action mediated in part through complement inhibition (50,60). However, heparin possesses other pharmacodynamic properties that could explain its cytoprotective actions. A comparison between heparin and an o-desulfated non-anticoagulant heparin with greatly reduced anti-complement activity administered at the time of coronary artery reperfusion in a canine model of myocardial infarction, equally reduced neutrophil adherence to ischemic-reperfused coronary artery endothelium, influx of neutrophils into ischemic-reperfused myocardium, myocardial necrosis, and release of creatine kinase into plasma (72). The authors report that heparin or o-desulfated heparin also prevented dysfunction of endothelial-dependent coronary relaxation following ischemic injury. In addition, heparin and o-desulfated heparin inhibited translocation of the transcription nuclear factor-kappaB (NF- κ B) from the cytoplasm to the nucleus in human endothelial cells and decreased NF- κ B DNA binding in human endothelium and ischemic-reperfused rat myocardium. Thus, it was observed that heparin and non-anticoagulant heparin decrease ischemia-reperfusion injury by disrupting multiple levels of the inflammatory cascade, including the novel observation that heparins inhibit activation of the proinflammatory transcription factor NF- κ B. That a similar mechanism(s) might apply to sulodexide is suggested by the many studies involving the anti-inflammatory actions attributable to a wide range of glycosaminoglycans (39,63).

It is understood that heparin and other GAGs have therapeutic uses beyond their traditional role as anticoagulants (63). The parenteral administration of sulodexide results in a decrease in myocardial infarct size in a model of *in vivo* regional ischemia/reperfusion (48). The results are in accordance with previous studies in which it was found that other glycosaminoglycans have the ability to reduce infarct size *in vivo* (6,29,34,47,70). The chemical composition of sulodexide is defined as 80% low molecular mass (7000 Da) heparin fraction and 20% DS. Low-molecular mass heparin contains the same dimeric components as unfractionated heparin, but has a lower degree of sulfation and shorter polysaccharide chain length. DS is a polysaccharide made up of many various disaccharide units with a mean molecular mass of 25,000 Da. As a result of the presence of both fractions, sulodexide potentiates the antiprotease activities of both antithrombin III and heparin cofactor II simultaneously. Although structurally similar, sulodexide has major differences from unfractionated heparin including prolonged half-life, reduced effect on global coagulation, and oral bioavailability (8,9). Low-molecular mass heparin has previously been shown to reduce infarct size following ischemia and reperfusion (34,51); however, DS has yet to be individually investigated. Due to their ability to inhibit the complement cascade, it is hypothesized that GAGs may prevent the adverse events associated with complement activation associated with ischemia/reperfusion. Activation of the complement cascade leads to the assembly of the MAC on cell membranes. Deposition of a sufficient number of the lytic membrane attack complexes on a nucleated target cell results in disruption of the cell membrane and ultimately cell lysis. Intravenous administration of 0.5 mg/kg sulodexide, commencing immediately upon reperfusion and at hourly intervals during reperfusion was associated with a significant decrease in myo-

cardial infarct size expressed as a percentage of the area at risk when compared with vehicle-treated control rabbits (48).

Analysis of platelet reactivity, as determined by *ex vivo* platelet aggregation, demonstrated a decrease in thrombin-induced platelet aggregation in platelet rich plasma prepared from whole blood obtained from sulodexide-treated animals as compared with vehicle-treated animals. These data agree with previously reported findings (13,63) that indicated that sulodexide inhibits thrombin-induced platelet activation. Interestingly, evaluation of the effects of sulodexide on coagulation, using the aPTT, demonstrated that at the dose found to be cytoprotective in the reperfused heart sulodexide produced little or no change in hemostasis (48).

As another method of quantifying cardiac injury after ischemia/reperfusion, we measured the serum concentration of a biochemical marker of tissue injury. Cardiac-specific troponin I (cTnI) is a component of the contractile machinery within myocytes. Upon cell lysis, the cardiac muscle protein is released into the blood and can be quantified using a specific immunoassay. As would be predicted, based on infarct size data, it was found that sulodexide significantly reduced the concentration of cTnI during reperfusion.

As is the case with other GAGs, the precise mechanism by which sulodexide achieves myocardial protection after ischemia/reperfusion remains to be determined. Since sulodexide affects several aspects of reperfusion injury, various hypotheses may be drawn concerning its role in cardioprotection. Previous studies have indicated that GAGs are effective inhibitors of the complement system. Therefore, we sought to investigate the likelihood that sulodexide acts to protect the myocardium through inhibition of the complement cascade.

C-reactive protein (CRP) is an acute phase protein that has been demonstrated to be a sensitive, but nonspecific, marker of inflammation. Not only is the plasma concentration of CRP increased in inflammatory diseases, increased CRP concentrations are associated with increased mortality due to cardiovascular events (78). Thus, CRP may be an indicator of myocardial injury, as well as being involved in the pathogenesis of irreversible myocardial injury (23,64,65,76,78). The proposed mechanism of CRP involvement is through local activation of the complement system (73,74). Systemic administration of human CRP was found to increase the extent of myocardial necrosis, through a complement-dependent mechanism, in an experimental model of acute myocardial infarction (36). The endogenous production of CRP in response to a remote inflammatory dermal lesion likewise resulted in an increase in the extent of myocardial injury after ischemia/reperfusion (5). CRP has been shown to activate the classical complement pathway providing a possible mechanism linking CRP to mortality due to myocardial infarction (44,55,75,77). Using an immunofluorescent method to determine the presence of tissue bound CRP and MAC, it was possible to show that sulodexide significantly reduced the deposition of both CRP and the MAC, which were found localized within the area of infarction. The results of this study demonstrate that sulodexide reduces infarct size after reperfusion of the ischemic myocardium. The mechanism by which sulodexide protects the myocardium appears to involve modulation of the complement cascade, possibly through the inhibition of CRP. Previous studies (48) provide evidence that there is a clear separation between the anticoagulant and anticomplement effects of glycosaminoglycans.

We showed that a dose of sulodexide, previously found to have little or no effect on coagulation (37) retains the ability to inhibit activation of the complement cascade and to

protect the ischemic myocardium. Therefore, sulodexide may have utility as a cytoprotective agent with a reduced risk of adverse effects on hemostasis.

Antiatherosclerotic and Antilipemic Effects

It is established that upon administration of heparin and low molecular weight heparin there is a release of lipoprotein lipase (12). Sulodexide also was demonstrated to be effective in bringing about the release of lipoprotein lipase activity after intravenous, subcutaneous or oral administration (19). Thus, sulodexide is often rated on its lipasemic activity (as Lipoprotein lipase Releasing Units, LRU). In cholesterol-fed rabbits, sulodexide significantly reduced the concentration of plasma cholesterol and cholesterol accumulation in the rabbit abdominal aorta compared to controls (62). The disappearance of radiolabeled low-density lipoproteins was enhanced after addition of sulodexide in rat liver perfusates of healthy, lipidemic or hypertriglyceridemic rats. Sulodexide was shown to interact with very low density lipoprotein by decreasing lipoprotein uptake into the rabbit aorta and by increasing the hepatic metabolism in normal and hypertriglyceridemic animals (21).

Diabetic Nephropathy

The incidence of diabetic nephropathy (DN) and correlated end stage renal disease in the United States is increasing (66) and the survival of renal disease patients on dialysis is low. DN involves the thickening of the glomerular basement membrane and mesangial expansion with hyalinosis, both in the mesangium and capillary lumen (32). The end result is fibrosis of the glomerulus, which disrupts the renal filtration unit and eventually results in renal failure. One of the first clinical markers of DN is microalbuminuria (54), either of hemodynamic origin (41), due to endothelial dysfunction (28), or biochemical, due to alteration in glomerular basement membrane GAG composition leading to abnormal permeability (24).

Glycemic control and angiotensin converting enzyme inhibitors are effective in reducing albuminuria and slowing the progression from DN to renal failure (25,49). However, new and innovative approaches to the prevention and treatment of DN are needed because strict metabolic control in the diabetic patient can be difficult. In addition, even diabetic patients responding to angiotensin converting enzyme inhibitor therapy and metabolic control show progressive renal damage and eventually develop end-stage renal disease (25,49).

GAGs are particularly interesting because they can repair endothelial lesions and the metabolic defect in matrix and basement membrane synthesis, which are responsible for DN (11,31,33). A loss of GAGs has been demonstrated in this condition and sulodexide was reported to be effective in the prevention of morphological alteration and in the reduction of albuminuria in experimentally diabetic animals (31). This behavior has been confirmed in humans with either type I or type II diabetes who were randomly assigned to 4 groups and administered different oral doses of sulodexide for 4 months, T4, and followed for additional 4 months, T8 (Table 1) (32). During treatment, the rate of albumin excretion decreased, but was found again to increase 4 months after cessation of treatment. Similarly, Achour et al. reported that in patients with type 1 and 2 diabetes mellitus treated with oral sulodexide (50 mg daily), albuminuria was significantly reduced compared to matched controls ($p = 0.0001$) (1).

TABLE 1. The effect of sulodexide on albumin excretion rate in Type 1 and Type 2 diabetic subjects

Treatment groups Dose of sulodexide (S), mg/day	Log Albumin Excretion Rate		
	T0	T4	T8
Placebo	5.10 ± 0.19	5.31 ± 0.11	5.07 ± 0.13
S, 50	4.62 ± 0.16	4.95 ± 0.12*	5.05 ± 0.13
S, 100	4.58 ± 0.17	4.63 ± 0.12**	4.73 ± 0.13
S, 200	5.25 ± 0.18	3.98 ± 0.11**†	4.11 ± 0.13**†

Two hundred and twenty three diabetic patients were allocated to the four study groups. Log albumin excretion rates were determined at baseline (T0), after four month sulodexide treatment (T4), and at four month follow up (T8). Values are expressed as log means ± S.E.M. Table was adapted with permission from the Diabetic Nephropathy and Albuminuria Sulodexide (Di.N.A.S.) randomized trial. * $p < 0.03$ vs. placebo; ** $p < 0.0001$ vs. placebo; † $p < 0.05$ vs. T0.

CONCLUSIONS

Sulodexide is a standardized extractive glycosaminoglycan containing 80% “fast moving” heparin and 20% dermatan sulphate. It has a high bioavailability after intramuscular, intravenous or oral administration. The agent is tolerated well in humans and in animals. Sulodexide has been shown to reduce infarct size and inflammation during reperfusion in animals with myocardial ischemia. The administration of sulodexide results in the release of lipoprotein lipase and has been shown to decrease the concentration of circulating lipids as well as to reduce the deposition of lipids in the vascular wall in experimental animals of hypercholesterolemia. Sulodexide has also been shown to slow the progression of diabetic nephropathy by reducing microalbuminuria. A review of the current literature demonstrates the efficacy, safety, and efficiency of sulodexide as an effective therapeutic intervention in peripheral arterial disease, cardiovascular events, in postphlebotic syndrome and on albuminuria in nephropathy without concern for adversely altering normal hemostasis.

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