Sulodexide (SLX) is a peculiar and interesting antithrombotic drug. It is a highly purified mixture of glycosaminoglycans (GAG) with anticoagulant and antithrombotic properties used for the prophylaxis and treatment of thromboembolic diseases. The pharmacological effects of SLX differ substantially from other GAG and are mainly characterized by a prolonged half-life and reduced effect on global coagulation and bleeding parameters. SLX is able to potentiate the antiprotease activities of both antithrombin III and heparin cofactor II. SLX shows also in vitro and in vivo profibrinolytic actions. SLX exhibits antithrombotic and profibrinolytic properties in several animal models of venous and arterial thrombosis and has relatively high affinity for endothelial cells. By oral route SLX is able to release tissue plasminogen activator and increase fibrinolytic activities. SLX is clinically effective in the treatment of peripheral arterial vascular diseases and in the treatment of deep venous thrombosis. SLX has also been found clinically active in the treatment of venous ulcers of the leg. SLX has been also used with success in tinnitus and in the thrombosis of central ocular vein. Recent data suggest that SLX could have beneficial effects in the treatment of diabetic nephropathy and in reducing microalbuminuria. However very recent multicentre trials conducted in this clinical setting have not confirmed this benefit of SLX. In this review we summarise the clinical data available regarding efficacy, safety and tolerability of SLX as antithrombotic agent. SLX is an effective drug for the treatment of peripheral arterial and venous vascular diseases. SLX is efficacious in the treatment of tinnitus and in the thrombosis of central ocular vein. Data regarding efficacy of SLX as nephro-protective drugs in diabetic patient with micro or macroalbuminuria are at the moment conflicting.

Key word: Sulodexide, glycosaminoglycans, antithrombotic drug, prophylaxis, thromboembolic.

INTRODUCTION

Sulodexide (SLX) is a highly purified mixture of glycosaminoglycans (GAG) composed of low molecular weight heparin (80%) and dermatan sulfate (20%) [1]. The low molecular weight of both SLX fractions allows for extensive oral absorption compared to unfractionated heparin [2]. The pharmacological effects of SLX differ substantially from other GAG and are mainly characterized by a prolonged half-life and reduced effect on global coagulation and bleeding parameters [3]. Due to the presence of both GAG fractions, SLX potentiates the antiprotease activities of both antithrombin III and heparin cofactor II simultaneously [4]. SLX shows also in vitro and in vivo profibrinolytic actions. The lipolytic activity of SLX is increased in comparison to unfractionated heparin [5]. Specially, oral administration leads to fibrinolytic activities in contrast to oral administration of other GAG. Thus, SLX releases tissue plasminogen activator and decreases fibrinogen levels as well as HDL and total cholesterol levels and blood viscosity [6]. Given orally, subcutaneously, or by intravenous injection, SLX exhibits antithrombotic and profibrinolytic properties in several animal models of
venous and arterial thrombosis and has relatively high affinity for endothelial (and possibly other) cells [7]. SLX 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 [8]. This antithrombotic and antithrombin activity is of great pharmacologic interest and makes SLX 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 SLX 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 SLX, whereas the high-density lipoprotein fraction increases [9]. Clinical studies have demonstrated the safety and efficacy of SLX. SLX is used for the prophylaxis and treatment of thromboembolic diseases; however, recent research has also demonstrated the beneficial effects of SLX in animal models of reperfusion injury and the treatment of diabetic nephropathy. In combination with Melatonin, SLX have been shown to be a viable treatment option for patients suffering from central or sensorineural tinnitus. Additionally, in a large multicenter clinical trial [10] involving 3986 patients who had recovered from acute myocardial infarction, oral SLX was associated with a 32% reduction in death and a significant reduction of left ventricular thrombus formation. Clinical efficacy of SLX has been demonstrated in peripheral arterial disease, cardiovascular events, in postphlebitic syndrome and on albuminuria in nephropathy. There is no interaction between SLX 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. SLX may become the treatment of choice when dealing with vascular diseases and their complications [11], 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 [12]. SLX is used in the treatment of a number of vascular disorders with increased risk of thrombosis, including intermittent claudication, peripheral arterial occlusive disease and post-myocardial infarction [13]. In this review we summarise the clinical data available regarding efficacy, safety and tolerability of SLX as antithrombotic agent.

**Sulodexide in Peripheral Vascular Diseases**

SLX 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 [14]. SLX has been extensively evaluated in patients with peripheral occlusive vascular diseases. A large number of clinical studies have been performed with SLX in this setting [15-17]. Several studies were double-blind placebo controlled trials. All studies included patients with Leriche-Fontaine stages I-III disease, ranging from no clinical symptoms to intermittent claudication and significant symptoms. Patients initially received IM SLX in general up to the first month followed by oral administration (60 mg/day) in the long term. Treatment with SLX 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 SLX.

**a) Peripheral Arterial diseases (POAD):** The aim of the trials evaluating the efficacy of SLX in this clinical setting were to look at the effect of SLX in diabetic [18] and non-diabetic patients [19] with peripheral occlusive arterial disease (POAD) if the drug affects the clinical course of claudication or the main risk factors for POAD. SLX increases the pain-free walking distance (benefit 36% vs. controls, P < 0.001). One meta-analysis [20], which has included all randomised controlled trials confirmed the effectiveness of SLX in improving claudication (lower limit of the 95% CI for overall odds ratio always >1). There was a marked effect in lowering triglycerides (overall -28%, P = 0.0015), fibrinogen (-13%, P < 0.0001) and plasma and serum viscosities, and in increasing high-density-lipoprotein cholesterol (24.4%, P = 0.0007). The medium-term administration of SLX has a therapeutic effect on claudication of diabetic and/or hyperlipidaemic patients suffering from POAD stages and also counteracts several POAD risk factors. Long-term use of SLX appears to be well tolerated [21]. The treatment has a low daily cost; therefore, it has a favourable cost-benefit ratio, in view of the high general costs associated with global POAD care, particularly in diabetic patients.

**b) Venous vascular Diseases:** Clinical trials have
demonstrated the beneficial effects of SLX in the treatment of deep vein thrombosis. Errichi et al. [22] 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. Also Cijureda et al. [23] have evaluated the effect of SLX in patients deep venous thrombosis. This study was carried out to assess the safety and efficacy of a fixed dosage of SLX compared to adjusted dosages (INR) of acenocoumarol as secondary prophylaxis in patients with deep vein thrombosis (DVT) in lower limbs. One hundred and fifty patients of both sexes were included, all over 18 years of age and diagnosed with proximal DVT of the lower limbs by color echo-Doppler, and with clinical evolution of less than 1 month. The patients were initially treated with low-molecular-weight heparin (LMWH) and urokinase in accordance with the established protocol. They were then randomized to continue treatment with acenocoumarol and INR adjustments every 30 days, or with SLX. Treatment was extended for 3 months with monthly follow-up visits and a final visit at 3 months post-treatment. In the group treated with sulodexide, no major/minor haemorrhagic complications were detected. On the other hand, in the acenocoumarol group, 1 major haemorrhage and 9 minor haemorrhages were produced (13.3%), reaching statistical difference in relation to the SLX group (p = 0.014; CI from 95% of 4.7% to 19.4%). The results of this trial proved the efficacy, safety, and efficiency of SLX as a secondary prophylaxis in thromboembolic disease, avoiding hemorrhagic risks and the monitoring of patients, and providing significant savings to the health system. Additional studies have evaluated the efficacy of SLX at doses of 50–100 mg/day administered for up to 24 months in patients with venous vascular diseases. Patients with deep vein thrombosis (DVT), varicose syndrome, and deep thrombosis were studied in a double-blind, placebo-controlled crossover study [24]. In this study SLX improved significantly the fibrinolytic potential of the treated patients with a significant reduction of circulating fibrinogen plasma levels. These results support the use of SLX in patients with venous disorders and at risk of thrombotic complications. Saviano et al. [25] in a multicenter, randomized, double-blind, double masked trial have studied patients with chronic venous insufficiency secondary to varicose syndrome or to a thrombotic episode confirmed by Doppler evaluation. Patients were treated with 50–100 mg/day of SLX for 60 days. The results demonstrate a significant improvement in venous pressure, assessed in the saphenous and tibial veins, with significant clinical improvement at the end of treatment, which can be attributed to the effect of SLX on thrombotic factors, ie, tPA, fibrinogen, and plasma viscosity, which was more rapid in patients receiving the higher SLX dose. SLX has 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 [26]. In patients with venous ulcer disease, Evidence base database suggest that SLX should be considered to be beneficial in the treatment of this vascular condition [27].

**Sulodexide in ENT and Ocular Vascular Pathologies**

SLX has been successfully used in the treatment of sensorineural tinnitus. Neri et al. [28] have evaluated in 102 patients suffering from tinnitus the efficacy of S in association with melatonin in a randomised controlled study. S was effective in improvement Tinnitus Handicap Inventory and Acufenometry score in comparison with control group. SLX was studied also in patients with vascular origin vertigo. SLX 250 LSU bid for 2 months showed a clinical efficacy in this condition with a significant improvement in symptoms and clinical presentation. Case reports have shown that this molecule is effective in patients with central ocular vein thrombosis [29].

**Sulodexide in Diabetic Nefropathy**

Recent researchs have demonstrated the beneficial effects of SLX in the treatment of diabetic nephropathy [30]. SLX is composed of the two GAGs that are active in preventing diabetic nephropathy in the experimental model [31]. Therefore SLX has emerged as a potential treatment of DN as multiple studies have demonstrated reductions in urinary albumin excretion with glycosaminoglycan therapy. Gambaro et al have [32] evaluated the effect of SLX in patients with diabetic nefropathy. A 4-mo course of high doses of SLX significantly and dose-dependently improved albuminuria in DM1 and DM2 patients and micro- or macroalbuminuric patients with or without concomitant ACE inhibition. The effect on albuminuria was long-lasting and seemingly additive to the ACE inhibitor effect. In the DiNAS study, a randomized, double-blind and placebo controlled trial, a total of 223 patients with DMT1 or DMT2 and microalbuminuria or macroalbuminuria were enrolled. Patients were randomized to receive SLX (50 to 200 mg daily) or placebo for 4 months. After 4 months of therapy, albuminuria decreased by as much as 74% compared with the placebo group. Four months after drug discontinuation, albuminuria remained 69% lower in
those randomized to 200 mg of SLX compared with the placebo group. This sustained response suggests that some anatomical or structural changes had occurred with SLX treatment. SLX was well tolerated in that study. A study conducted by Lewis et al. [33] however did not confirm these data. The Sun Micro trial, a multicenter placebo-controlled double-blinded study was performed to determine the effect of SLX on urine albumin excretion in patients with type 2 diabetic nephropathy. The primary end point was normoalbuminuria (ACR <20 mg/g and a decrease >25%) or 50% decrease in baseline ACR. In 1,056 randomly assigned patients comparing the SLX versus placebo groups, the primary end point was achieved in 16.5% versus 18.4%; normoalbuminuria, in 7.9% versus 6.1%; and a 50% decrease in albuminuria, in 15.4% versus 17.6%. The relative probability of any given change in albuminuria was identical in both groups. In the SunMicro trial therefore sulodexide failed to decrease urine albumin excretion in patients with type 2 diabetic nephropathy and microalbuminuria. More recent data of a multicentre study (SunMacro trial) [34] show data SLX fails to exert a protective effect in diabetic nephropathy and macroproteinuria. This trial, which evaluated the renoprotective effects of SLX in patients with type 2 diabetes, renal impairment, and significant proteinuria (>900 mg/d) already receiving maximal therapy with angiotensin II receptor blockers. The primary end point was a composite of a doubling of baseline serum creatinine, development of ESRD, or serum creatinine ≥6.0 mg/dl. The study was planned to enrol 2240 patients over approximately 24 months but terminated the study after enrolling 1248 patients. After 1029 person-years of follow-up, the investigators did not detect any significant differences between SLX and placebo; the primary composite end point occurred in 26 and 30 patients in the SLX and placebo groups, respectively. Side effect profiles were similar for both groups. In conclusion, the results of SunMacro trial does not suggest a renoprotective benefit of SLX in patients with type 2 diabetes, renal impairment, and macroalbuminuria. Taking in account the data, there are not convincing evidence that SLX could have a nefroprotective action.

Conclusion

SLX, a glycosaminoglican with a mechanism of action similar to heparin, is an interesting therapeutic compound with anticoagulant, antithrombotic and profibrinolytic activities [35]. SLX is well tolerated in humans and in animals. SLX has been shown to reduce infarct size and inflammation during reperfusion in animals with myocardial ischemia. The administration of SLX 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. SLX has also been shown to slow the progression of diabetic nephropathy by reducing microalbuminuria. Several controlled randomised trials have evaluated the efficacy, safety, and efficiency of SLX in patients with peripheral arterial disease, prevention of deep venous thrombosis, cardiovascular events, tinnitus and vascular-induced vertigo, in postphlebitic syndrome. SLX is able to improve microalbuminuria in nephropathy patients without concern for adversely altering normal haemostasis. However very recent multicentre trials conducted in this clinical setting have not confirmed this benefit of SLX. The available clinical studies have shown that SLX is an effective drug for the treatment of peripheral arterial and venous vascular diseases. SLX is efficacious in the treatment of tinnitus and in the thrombosis of central ocular vein.

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