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Use of sulodexide for the treatment of disorders of peripheral microcirculation in patients with systemic sclerosis

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Abstract

Scleroderma (systemic sclerosis, scleroderma) is a chronic, progressive autoimmune disease characterized by damage to blood vessels, the presence of autoantibodies, progressive hardening, atrophy of the skin and subcutaneous tissue and damage to many internal organs. In scleroderma we observe peripheral microcirculation disorders, in which small peripheral vascular abnormalities play an important role. Raynaud's phenomenon is the most common manifestation of peripheral microcirculation disorders in the course of systemic sclerosis and concerns mainly the fingers. Treatment of patients with systemic sclerosis should be comprehensive and include education of patients, use of medication and rehabilitation. Drugs of first choice for the treatment of peripheral microcirculation disorders include calcium channel blockers, phosphodiesterase inhibitors, and prostaglandins. From our clinical experience gained in the treatment of microvascular disorders, sulodexide [a mixture of heparin (80%) and dermatan sulfate (20%)] seems to be a good and safe drug worth recommending. It works as an anticoagulant, pro-fibrinolytic, anti-inflammatory, inhibits the fibrosis process, and has protective effects on the vascular endothelial cells. Sulodexide is a safe rheological drug successfully used to treat a number of diseases accompanied by microcirculation disorders, including scleroderma.

Key words: sulodexide, systemic sclerosis, microcirculation disorders, rheological treatment

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Definition

Systemic sclerosis (SS) is an autoimmune, chronic, multisystem connective tissue disease characterized by damage to blood vessels, the presence of autoantibodies, progressive hardening of the skin and subcutaneous tissue and damage to many internal organs. In the more severe course of systemic sclerosis, internal organs such as the cardiovascular system, lungs, gastrointestinal tract, kidneys, central nervous system, the bone-joints and muscles can be affected [1].

Based on the severity and extent of skin sclerosis and clinical course, there are two main forms of systemic sclerosis: *diffuse systemic sclerosis* and a form of *limited systemic sclerosis* [2]. In the form of limited systemic sclerosis, scleroderma skin lesions are limited to the distal extremities and face; the clinical course is usually slow; organ complications occur in the later stages of the disease; and the prognosis is quite good. Diffuse systemic sclerosis is generally characterized by extensive skin lesions, which include not only the distal sections of limbs, but can also spread to the arms, thighs and torso. The clinical course of this form of the disease is dynamic, especially in its early years, with serious organ complications, which can appear quite early. Systemic sclerosis is characterized by a considerable diversity of clinical courses resulting from the differences in range and pace of development of organ damage in

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individual patients, in the course of which there is a dysfunction of the function and morphology of blood vessels accompanied by nonspecific inflammation and progressive fibrosis tissues.

Pathophysiology

One of the most important aspects of the pathogenesis of scleroderma is damage to the blood vessels. Changes observed in the early stage include activation and damage to vascular endothelial cells. These changes are accompanied by inflammation, which involve among others, monocytes, lymphocytes and fibroblasts with the deposition of extracellular basic substance in the skin and internal organs. As a consequence of chronic inflammation and progressive multiple sclerosis, the vascular wall reaches constriction, or even microvascular occlusion. Stenosis of blood vessels results in tissue ischemia [3].

Many authors indicate that a key role in the development of complex disorders of peripheral microcirculation observed in scleroderma is played by abnormalities of small peripheral vessels (small arteries, arterioles and capillaries), which often precede the development of the disease and are an important part of the early stage of systemic sclerosis [4]. Initially there is a formation of cavities between the endothelial cells and losing its continuity, as well as the formation of numerous vacuoles in the cytoplasm of endothelial cells. Damage to the endothelium and basement membrane leads to intravascular blood coagulation and platelet activation. This leads to the release of platelets and endothelial cells of many biological active substances responsible for the proliferation of intimal vascular smooth muscle cells [5]. Vascular changes in the course of SS may concern any internal organ, but most frequently diseased organs include: skin, lungs, heart and kidneys. As a result, damage to the endothelium in the course SS causes increased release, which further potentiates vasoconstriction and aggravates ischemia such as endothelin, thromboxane, vascular endothelial growth factor (VEGF) or thrombomodulin. On the other hand, it is deficient in factors such as vasodilator nitric oxide or prostacyclin [3].

The most common manifestation of peripheral microcirculation disorders in the course of scleroderma is Raynaud's phenomenon. It concerns mainly the fingers and rarely occurs in other locations. In the course of Raynaud's phenomenon, three characteristic phases can be observed. The first phase is blanching, with a sudden vasospasm and ischemia of the tissues accompanied by a feeling of pins and needles. This is followed by a blue effect due to the accumulation of deoxygenated blood, which patients describe as the feeling of numbness and pain (Fig. 1). The third phase is that of active congestion, distinguished by the redness of the skin and a burning sensation. Sometimes Raynaud's phenomenon is expressed only in two phases: blanching and bruising or bruising and redness [6]. The results of ischemia are often ulceration and scarring at the thimble joint of the fingers, nail failure (Fig. 2), necrosis and resorption or shortening, and consequently auto-amputation of distal phalanges (Fig. 3). In the course of peripheral microcirculation disorders, patients often report a feeling of tingling, numbness, and pain, waves of hot and cold feelings, and an abnormal sensation deep in the range of the distal limbs. This is an important cause of reduced quality of life among patients, affecting their daily activities and professional work.

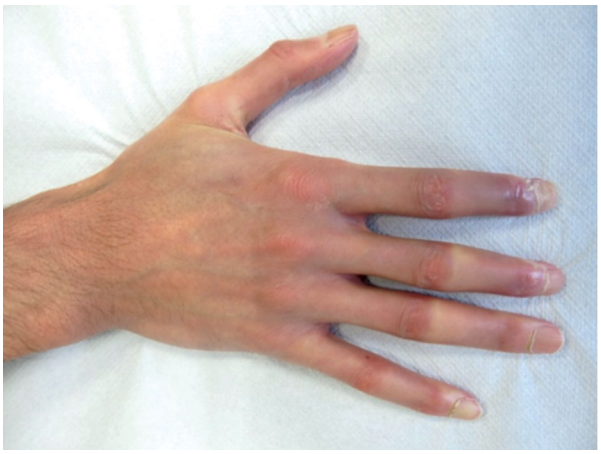

Figure 1. Raynaud's phenomenon

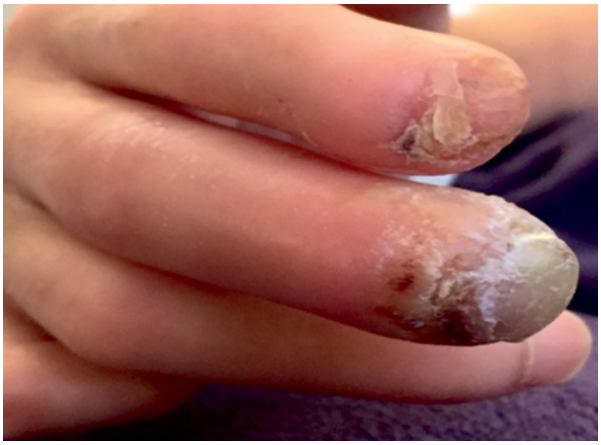

Figure 2. Scarring of the fingers, nail failure

One of the methods for assessing microcirculation is capillaroscopy, which allows morphological evaluation of the loop capillary in the skin. It enables assessment of structural and morphological portions of the test vessel.

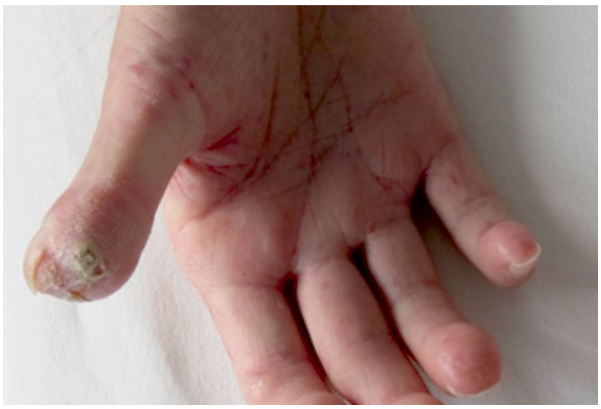

Figure 3. Thumb shortening

The most commonly observed places are shafts of the fingernails. The state of the nail plate, the background image, and the number, quality and distribution of the loop capillary should be assessed. Moreover, the assessment of the morphological types of capillary loops, their tension and blood flow through the loops should be carried out. Evaluation of the presence of avascular fields is also necessary [7].

Treatment

Treatment of patients with systemic sclerosis should be comprehensive and include education of the patients and the family, medical treatment, rehabilitation, and, if necessary, surgical treatment. Therapeutic treatment should be determined individually, depending on the form, severity and duration of illness, presence of organ damage (i.e. organ-specific strategy) and an individual assessment of the balance of potential benefits and risks of a particular treatment. Currently there are no drugs that inhibit the course of the disease in all patients with scleroderma (disease-modifying drugs) [1].

Drug-free treatment of peripheral microcirculation disorders is mainly based on the reduction of the factors intensifying the ailment. It is recommended that exposure to cold or stressful situations, as well as excessive or ambient temperature variations should be avoided. These include the wearing of warm clothes and the use of techniques that stimulate blood circulation, such as warming the hands and exercising the limbs. Attention should be paid to avoid smoking, drinking beverages with caffeine and taking certain medicinal substances (ephedrine, oral contraceptives).

Pharmacological treatment is recommended for patients with organ damage, as well as patients with Raynaud's phenomenon, who fail to respond to non-pharmacological treatment and suffer a high incidence of seizures.

According to the EULAR 2016 guidelines, first-line drugs in the treatment of disorders of peripheral microcirculation with proven effectiveness are dihydropyridine derivatives, i.e. nifedipine (30–60 mg/24 hours after), and sildenafil (selective inhibitor of phosphodiesterase type 5), which improve the healing of ulcers in patients with systemic sclerosis. In case the abovementioned treatment is ineffective in patients with finger ulcers and/or critical limb ischemia, prostanoids can be used, i.e. iloprost (0.5–3.0 ng/kg/min *i.v.* for 1–5 days every 6–8 weeks or 50–150 μg after 2 times a day). There are single studies showing the efficacy of fluoxetine (a selective serotonin reuptake inhibitor, 20 mg/24 hours *p.o.*), especially in patients who are nifedipine, sildenafil and prostaglandins intolerant. Bosentan (an endothelin receptor antagonist), which is used in the treatment of primary pulmonary hypertension in scleroderma at a starting dose of 62.5 mg 2 times a day for four weeks followed by 125 mg 2 times a day for 12 or 20 weeks, has proven to be effective in preventing the formation of new ulcers. During treatment with these drugs, attention should be paid to the possible and quite frequent side effects such as headaches, dizziness, and hypotension. Among patients with pulmonary arterial hypertension, a particularly severe (grade III–IV) first-line drug is epoprostenol in an initial dose of 2 ng/kg/min, *i.v.*, which improves the functional lung volume and hemodynamic parameters. To consider the treatment of pulmonary hypertension guidelines, authors indicate prostacyclin analogues (iloprost, treprostinil) and endothelin antagonists (ambrisentan, bosentan, MACITENTAN) PDE-5 inhibitors (sildenafil, tadalafil) and riociguat (a stimulator of guanylate cyclase). Despite a number of adverse effects, cyclophosphamide (1–2 mg/kg/day p.o.) has been recommended for patients with progressive pulmonary fibrosis.

Methotrexate is a drug used to treat skin sclerosis, especially at an early stage. In the case of nephropathy, individual studies indicate an enhanced survival rate among patients treated with angiotensin-converting-enzyme inhibitors. At the same time, it is believed that glucocorticoids used to treat scleroderma may impair kidney function. In the case of gastrointestinal complications, it is recommended that the use of proton pump inhibitors (GERD, gastric ulcer prophylaxis), prokinetics (dysphagia, GERD, flatulence, etc.) and antibiotics (in symptomatic bacterial infection of the small intestine). Use of a formulation of mycophenolate mofetil in the treatment of organ damage in systemic sclerosis is still the subject of many studies. Hope for patients with systemic sclerosis may lie in biological therapy with tocilizumab (162 mg/week *s.c.*), which is currently undergoing clinical trials [8].

As an alternative, and/or supporting method of SS treatment, oral or parenteral infusion of sulodexide can be applied. Sulodexide is a purified mixture of glycosaminoglycans obtained from bovine intestinal mucosa, comprising a heparin of a rapidly moving field of electrophoresis (80%) and dermatan sulfate (20%). These substances occur naturally in the human body and have a high affinity to endothelial cells, as evidenced by their rapid binding with the surface of these cells after introduction into the bloodstream. Fast moving heparin (FMH) electrophoresis has affinity for antithrombin III, while the dermatan sulfate has affinity for heparin cofactor II, which results in the anticoagulant effect of sulodexide. FMH differs from the nonfractional heparin and slow moving heparin with lower molecular weight, smaller number of sulphate groups and weaker anticoagulant activity [9]. The potential impact of sulodexide on endothelial cells suggests that it may modify not only anticoagulant or fibrinolytic activity, but also other properties of these cells. Sulodexide reduces intravascular inflammation and suppresses the inflammatory response in endothelial cells, causing a transient increase in the concentration of HGF, which is a potent anti-inflammatory cytokine and reduction of interleukin-6 [10]. There is evidence that sulodexide lowers plasma lipid levels. It also affects the inhibition of intracellular oxidative stress [11]. Endothelial cells line all blood vessels, and their total area in the human body is ca. 4000–7000 m^2. The endothelium provides liquidity for blood, reduces the influence of the cellular components of blood from the vessel wall, regulates the amount of blood flow through the vessel, and also provides the dynamic barrier that enables communication between the intravascular space and extravascular space while delimiting these spaces. Endothelial surface is coated with a mixture of glycoproteins and glycosaminoglycans, identified as the glycocalyx. The composition of this structure includes, inter alia, heparan sulfate, which is a cofactor for thrombin III, and dermatan sulfate impinging of heparin cofactor II. Endothelial cells regulate many endovascular processes, and affect peripheral blood flow through vasoconstrictional and vasodilatial activity, as well as providing a barrier that regulates the exchange of fluid and particles between the intravascular and extravascular space. The endothelium produces factors extending the walls of blood vessels (nitric oxide, prostacyclin, endothelial hyperpolarizing factor) and shrinking factors (thromboxane A_2, prostaglandin F, prostaglandin H, endothelin). Sulodexide was successfully applied to a number of diseases related to disorders of endothelial cells. Previous studies have shown the beneficial effect of sulodexide in patients with hepatic microcirculation in diabetes (preventing prooxidant and proinflammatory effects of hyperglycemia on the endothelium) [12, 13], the prevention of atherosclerosis (slow structural and functional changes in endothelial cells) [14]. Antithrombotic activity of the drug in patients after myocardial infarction has been proven. In peritoneal dialysis patients, limitation of transperitoneal protein loss after chronic administration of sulodexide to the dialysis fluid was observed [15]. This medicine is used to treat vascular dementia, venous thrombosis, venous insufficiency and leg ulcers [16] as well as lowering blood pressure [17].

In the Dermatology Department, Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw alprostadil and sulodexide are basic drugs used to treat rheological patients with scleroderma.

Alprostadil is a combination of prostaglandin E_1 with α-cyclodextrin in a 1:1 ratio. This drug dilates blood vessels — arteries and sphincters, decreases aggregation and platelet activation, increases plasma fibrinolytic activity, increases the ability to deform erythrocytes, stems activation of neutrophils and proliferation of myocytes, thus preventing tissue damage in inflammatory and ischemic processes. It improves cellular metabolism by increasing the supply and utilization of oxygen and glucose in ischemic tissue [18]. The therapy consists of intravenous infusion of 60 μg of the preparation (1 ampoule of 60 μg dissolved in 50–250 mL of 0.9% natrium chloride in continuous infusion) for 3 hours once a day for 3 days at intervals of 6–10 weeks.

Based on the experience of our Clinic in patients with peripheral microcirculation disorder in systemic sclerosis, who experience side effects or contraindications to parenteral treatment with prostaglandins, a parenteral preparation of 600 LSU/2 mL sulodexide (1 ampoule) is administered twice a day every 6 hours with good general tolerance. In addition to sporadic cases of dizziness and hypotension, no side effects are observed. Improved peripheral microcirculation, i.e. reduction in the frequency of seizures, hand numbness, and freezing of the hands.

During parenteral treatment with sulodexide, it is important to discontinue the use of heparin and oral anticoagulants to reduce the risk of bleeding.

In addition to parenteral treatment, sulodexide is successfully used in outpatient treatment programs, where capsules for all patients with systemic sclerosis and with peripheral microvascular disorders are administered (one capsule twice a day).

Sulodexide is used in addition to other rheologic drugs, among others with calcium channel blockers and phosphodiesterase inhibitors or as a monotherapy, if there are contraindications or intolerances of the abovementioned drugs.

Summary

Sulodexide is a safe rheological drug successfully used in a number of diseases characterized by circulatory disturbances with a negligible amount of side effects observed. Antithrombotic, pro-fibrinolytic, antinflammatory, fibrosis inhibiting and protective action with regard to the vascular endothelial cells makes sulodexide a drug with a potentially broad spectrum. Another factor is that the composition comprises a naturally occurring molecule in the body of glycosaminoglycans present in glycocalyx endothelial cells.

According to our knowledge and based on an analysis of the literature, we find that in cases of patients with impaired peripheral microcirculation, a manifestation in the form of erosions, ulcers phalanges in distal hands and Raynaud's phenomenon in the course of scleroderma, a regime of one ampoule of sulodexide every twelve hours for 3 to 4 days every 4–6 weeks (one of the possible production schemes) is effective and should be recommended for the treatment of vascular complications of systemic sclerosis.

In order to determine the best tolerated effective dose and protocol for the administering of intravenous infusion, further studies are needed into the control group of patients with systemic sclerosis and severe disorders of peripheral microcirculation.

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