Clinical Benefits of Daflon 500 mg in the Most Severe Stages of Chronic Venous Insufficiency

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Chronic venous insufficiency (CVI) affects a large number of people in Western countries, and is responsible for considerable inconvenience, discomfort, suffering, and costs.

Micronized purified flavonoid fraction (MPFF, 450 mg diosmin plus 50 mg hesperidin-Daflon 500 mg) is a potent venotropic drug used in the treatment of venous insufficiency. Pharmacological and clinical studies demonstrated the comprehensive mode of action of Daflon 500 mg: it increases venous tone, it improves lymph drainage, and it protects the microcirculation. Clinical international, prospective, multicenter, randomized, controlled studies versus placebo studies documenting the effects of Daflon 500 mg in CVI at advanced stages with edema, skin changes, and venous leg ulcer are reviewed. In edema, one of the most frequent complaints of patients, Daflon 500 mg brings about a significant reduction in leg circumference, thanks to its capacity to inhibit inflammatory reactions and to decrease capillary hyperpermeability. The rationale for the use of Daflon 500 mg for treatment of skin disorders and venous leg ulcer is its action on the microcirculation-damaging processes. Regarding skin changes, Daflon 500 mg has been shown to improve venous trophic disorders, like gravitational (stasis) dermatitis, and dermatofibrosclerosis. In venous leg ulcer, Daflon 500 mg's clinical efficacy has been demonstrated in addition to standard treatment or versus standard treatment alone.

Daflon 500 mg, thanks to its comprehensive mode of action on the veins, lymphatics, and microcirculation, is the method of choice not only in the early stages of CVI treatment, but also in the severe stages of this condition, in combination with compression treatment, sclerotherapy, and surgery if appropriate.

Introduction

Chronic venous insufficiency (CVI) has been defined as "all changes resulting from dilatation of the veins of the lower limbs, incompetence of their valves, and resultant venous hypertension."[1] It is a congenital or acquired functional abnormality, which may or may not be accompanied by an obstructive syndrome. Venous insufficiency may be superficial, deep, or mixed. It starts early in life: 10% of the schoolchildren in the Bochum study,[2,3] aged between 10 and 12 years, had slight varicose veins. In the adult population in Europe, venous disorders may affect 25% to 50% for all types and degrees of varicose veins, 10% to 15% for marked varicose veins, and 5% to 15% for CVI.[4,5]

Skin changes are the cutaneous manifestations of venous insufficiency and essentially affect the lower third of the leg, where raised ve-

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nous pressure predominates. Skin changes mainly include gravitational dermatitis, hyperpigmentation ("dermite ocre"), atrophie blanche, and also edema, mostly due to increased capillary permeability. Many of these disorders occur following development of varicose veins.

In population surveys of varicose veins, edema was found to be the most common manifestation: 19.7% of subjects with varicose veins of any severity in Brazil,[6] 20% of women and 10% of men in Tecumseh (USA).[7] In the 11-year follow-up of chemical workers in the Basle study, the percentage of subjects developing complications depended on the severity of varicose veins. For those with mild varicose veins, 17% developed edema, compared with 30% of those with severe varicose veins.[8] In the Basle Study (II), the prevalence of "pronounced" skin changes (dilatation of subcutaneous veins, hyperpigmentation or hypopigmentation) was found in 9.6% of women and 8.7% of men.[9] The prevalence increases markedly with age, so that in women only 1.8% of those aged 30 to 39 years had skin changes compared with 20.7% of those over 70 years of age.[7]

Venous leg ulcer is the most severe expression of chronic venous disease and is placed in the most advanced categories of the CEAP classification,[10] both from the clinical point of view (C5 for a healed ulcer and C6 for active ulcer) and in terms of invalidity score: active ulcers are assigned 9 points on the latest CEAP venous clinical scoring system (VCSS), which consists of a total of 30 points.[11]

Venous ulcers are a common condition in Western countries. Women are affected most often (3/1),[12] partially because of their greater longevity. A review of the results from several epidemiologic surveys of the general adult population over 18 years of age in Western countries has been undertaken.[8] An approximate estimate of the prevalence of open venous ulceration is 0.3%, and about 1 in more than 300 adults may have a leg ulcer at any one time. The population prevalence of open and healed ulcers combined could be more than 1%. The prevalence of venous ulceration increases consistently with age in both men and women: from 0.1% at any age below 60 years to nearly 0.4% for those aged 61 to 70 years, and more than 2% for those aged over 80 years, as reported in previous studies.[13] In a rural village in Sweden with 4,000 inhabitants, a total prevalence of nonhealed and healed ulcers of 12.6% was reported in the population aged 70 years and above.[14]

Venous disorders weigh heavily on health care budgets. Studies in the former Federal Republic of Germany showed that the total costs of varicose veins and phlebitis were estimated to be close to DM 2 billion (including hospitalization, outpatient treatment, medicines, private insurance, time off work, and sickness benefits).[15] The annual cost of venous leg ulcer alone is evaluated at 2% of the health care in the UK.[16] In a medicoeconomic study conducted between 1997 and 1998 in France, mean cost was 5,827 FF per patient: 48% for care, 33% for drugs, 16% for hospitalization, and 3% for sick leave from work.[17]

Pathophysiology

In CVI, the major pathological event is venous hyperpressure. Venous hyperpressure is a consequence of venous reflux caused by venous valvular insufficiency. Valve failure may be primary or secondary to deep venous thrombosis and may be located in 1 or more of the superficial veins, the perforator veins, or the deep veins. In up to 50% of patients with venous leg ulcer, their venous hypertension is attributable to superficial venous incompetence alone.[18] This is fortunate because such superficial reflux can be the target for direct surgical intervention using conventional techniques.[19] The actual causes of venous insufficiency remain unknown, with the exception of the postthrombotic syndrome, where there is clear evidence of vessel abnormalities and of valve destruction. CVI—whether primary because of decreased venous tone or valve failure, or secondary because of deep venous thrombosis, and whether it affects the superficial or deep veins—is linked to venous hyperpressure.

The high venous pressure, either in the superficial or in the deep venous system, overloads the capillary network,[20] which is the crucial factor in the pathogenesis of all the complications of venous disorders.

The importance of microcirculatory changes in severe complications of venous disease has been stressed.[21,22] The main pathophysiologic feature appears to be the activation of the leukocytes, followed by margination and interaction of these cells with the macrovascular endothelium, resulting in the preferential accumulation of neutrophils in the tissue. This initiates an inflammatory response releasing free radicals and other cy-

totoxic substances that may lead to tissue destruction and ulceration and, clinically, to the chronic changes seen in stasis dermatitis.

The application of measures such as the treatment of varicose veins, compression therapy, and administration of phlebotropic drugs may reverse or stop the inflammatory process.

Daflon 500 mg is a venotropic drug that is composed of micronized purified flavonoid fraction (MPFF), a semisynthetic micronized preparation of the γ-benzopyrone family consisting of 90% diosmin and 10% hesperidin. Daflon 500 mg improves venous tone[23-26] and decreases the inflammatory response[27-31] seen in the microcirculation. The drug has an excellent safety profile, as documented by both toxicologic animal studies and by clinical studies.[32] Several studies, performed in a large number of patients, have indicated its strong efficacy on the symptoms of venous disease.[33-38] The symptoms that have been investigated include heaviness, discomfort, itching, cramps, pain, and swelling.

This paper reviews the clinical studies documenting the effect of Daflon 500 mg in CVI at advanced stages with edema, skin changes, and venous leg ulcer.

Studies on Leg Edema

Edema is a basic sign in CVI that causes considerable discomfort to the patients, so that it is a frequent reason for consultation. Edema represents class C3 of the CEAP clinical classification.

In a double-blind, controlled, randomized trial conducted versus placebo, 200 patients with functional or organic venous insufficiency were included and treated with Daflon 500 mg or placebo. After 2 months of treatment, a significant reduction in ankle circumference was found in the patients who received Daflon 500 mg.[33]

The reduction in leg edema with Daflon 500 mg, 2 tablets daily, was also demonstrated in another study in which the reduction was assessed by volumetric measurement after 6 weeks of treatment.[34] In this study, the reduction in the mean volume was 263 mL (8%) in all patients, and was 392 mL (12%) in patients with leg edema associated with varicose veins. In both cases, this reduction in leg volume was highly statistically significant ($p < 0.001$).

In the Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids in chronic venous insufficiency (RELIEF) Study,[35] with 3,101 patients included, a significant reduction in leg edema was obtained by measuring leg circumference with the use of a standardized method: the Leg-O-Meter, which allows repetitive measurements at the same height. The 2 groups of patients, with and without venous reflux, were assessed at baseline and then every 2 months until the end of the study. Each group received Daflon 500 mg, 2 tablets daily, for 6 months. In both groups of patients, leg circumference was significantly reduced from the beginning of the treatment, and this reduction was progressive until the end of the study (Figure 1).

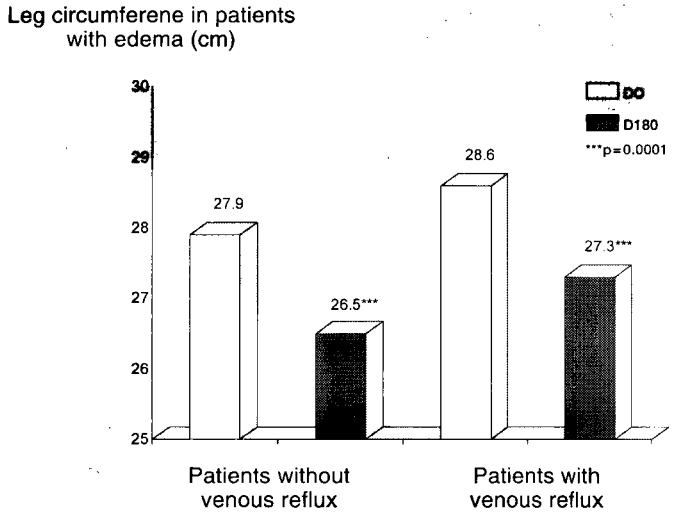

Figure 1. Significant decrease in leg circumference on treatment with Daflon 500 mg. Leg circumference, measured by the Leg-O-Meter, significantly decreased with Daflon 500 mg in both groups of patients, with or without venous reflux (patients in class 3 and 4 of the CEAP). Adapted from reference 35.

CVI-associated edema is characterized by increased venous permeability due to capillary hyperpressure acting upon the endothelial cells. Daflon 500 mg has demonstrated, by means of the "Landis isotope test,"[36] a protective effect on capillary vessels. These pharmacologic properties may explain the results obtained in clinical trials focused on the relief of edema.

Studies on Trophic Skin Disorders

Trophic skin disorders, such as gravitational dermatitis, atrophie blanche, hyperpigmentation, and dermatofibrosclerosis, represent a more advanced condition of CVI (C4 in the CEAP clinical classification). Their presence mirrors microcirculatory disorders. In many studies, the presence of skin changes is not assessed or is not used as an outcome of treatment.

Daflon 500 mg has been shown to improve skin changes in a clinical trial[37] carried out in 36 patients suffering from trophic disorders of the lower limbs related to CVI. This was a double-blind, placebo-controlled study. The treated group received Daflon 500 mg, 2 tablets daily, for 2 months. In 88% of patients treated with Daflon 500 mg, a significant improvement or resolution of reversible trophic disorders, such as gravitational eczema and inflammatory reactions, was observed, compared with only 21% in the placebo group (Figure 2).

In a clinical study[38] including 3,240 women presenting with dermatofibrosclerosis (n = 170), gravitational dermatitis (n = 42), or leg ulcers (n = 32), Daflon 500 mg, 2 tablets daily over 2 months, was shown to be a valuable therapy, improving all venous trophic disorders. CVI skin changes improved after 2 months of treatment in 46% of patients presenting with dermatofibrosclerosis and 66% with gravitational dermatitis. The healing of venous leg ulcers was improved in 62% of patients. Besides, a reduction in erythrocyanosis was shown in 69% of patients who presented with this sign at baseline (n = 536).

The rationale for the use of Daflon 500 mg in the treatment of complicated CVI is its protective effect on the microcirculation against inflammatory mediators.

A number of experiments have shown definite evidence of neutrophil and monocyte activation in response to venous hypertension,[21,22] which leads to microcirculatory disorders. During these processes, an interaction between the white blood cells and the endothelium starts: endothelial adhesion molecules, such as selectins (E, L, and P), integrins, intercellular adhesion molecules (ICAM), and vascular cell adhesion molecules (VCAM), are released from leukocytes and the endothelium. These substances favor the adhesion of leukocytes to the endothelium, and in turn cause injury to the endothelial cells.

Coleridge Smith et al[39,40] recently published results of a trial whose aim was to determine the effects of Daflon 500 mg on surface expression of leukocyte adhesion molecules (CD62L or L-se-

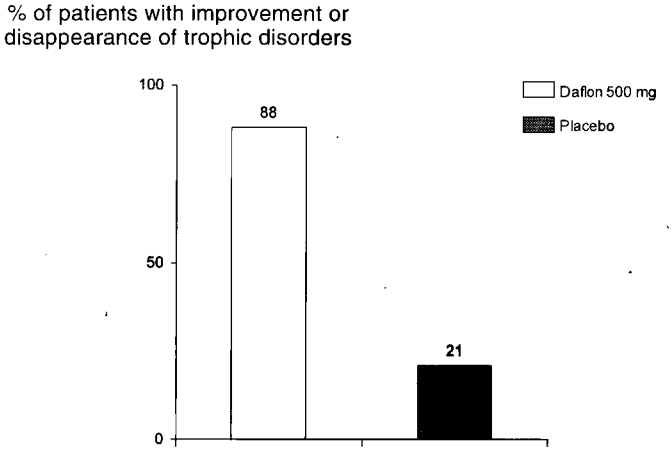

Figure 2. Significant improvement in trophic changes in 88% of cases on Daflon 500 mg versus 21% on placebo, after 2 months of treatment. Adapted from reference 37.

lectin and CD11b or integrin) in chronic venous disease. Patients affected by CVI classes C2 to C4 according to the CEAP clinical classification were enrolled in the study. After 60 days of treatment with Daflon 500 mg, the neutrophil level of CD11b and the neutrophil/monocyte level of CD62L significantly decreased, demonstrating the inhibition of leukocyte adhesion and activation. In this study, several patients reported improvement in their venous skin changes during the treatment, although these were not measured quantitatively.

Studies on Venous Leg Ulcers

Venous leg ulcer is the most severe expression of CVI and is due to complete failure of the compensatory pathophysiological mechanism of the microcirculatory system.

In animal studies, Daflon 500 mg has been shown to suppress postischemic leukocyte/endothelial cell interactions that are similar to the processes thought to lead to venous ulceration.[30,41] However, the final evidence that this drug's effect has clinical implications comes from the ability of the drug to facilitate venous ulcer healing in patients.

In a multicenter double-blind, randomized, placebo-controlled study,[42] the efficacy of Daflon 500 mg was demonstrated in improving healing of venous leg ulcers. One hundred and seven patients suffering from active venous ulcers were included in this study. They were divided into 2 groups, and received Daflon 500 mg, 2 tablets daily, or placebo in combination with standard therapy (both local therapy and conventional compression therapy). After 2 months of treatment, the percentage of complete ulcer healing in the Daflon 500 mg group was significantly higher than that of the placebo group: 31.8% of healed venous ulcers in the Daflon 500 mg group compared with 12.8% in the placebo group. Daflon 500 mg combined with standard therapy healed 3 times more venous leg ulcers than standard therapy with placebo, and in a shorter time.

In the study by Glinski et al,[43] 140 patients with CVI and venous leg ulcers were enrolled to received standard compressive therapy plus external treatment alone, or 2 tablets of Daflon 500 mg daily in addition to the above-mentioned treatment for 24 weeks. Ulcers with a diameter of less than 3 cm were healed in 71% of the Daflon 500 mg group and in 50% of the standard therapy group. When the ulcer's diameter was between 3 and 6 cm, they were healed in 60% and 32% ($p < 0.05$) in the Daflon 500 mg group and the control group, respectively. As a whole, the group that received Daflon 500 mg had a significantly higher ulcer healing rate than the other group (46.5% versus 27.5%, $p < 0.05$) (Figure 3).

The beneficial effect of Daflon 500 mg has also been demonstrated in terms of the percentage reduction in ulcer area. The reduction in size was most prominent during the first 2 months of treatment, independently of initial ulcer size. This was also observed in patients with ulcers more

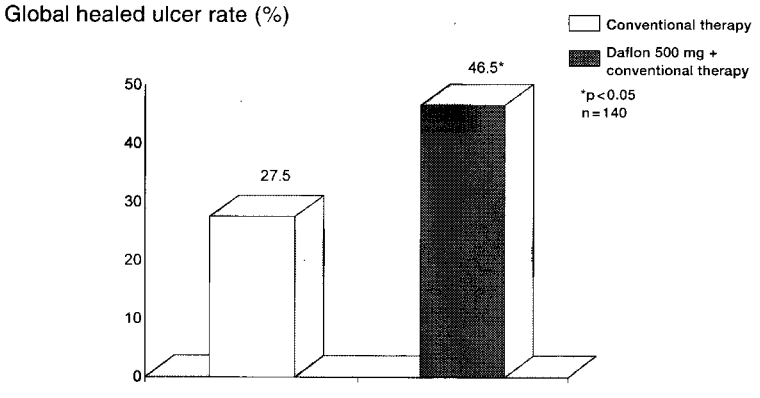

Figure 3. Daflon 500 mg, in addition to standard external and compression treatment, healed significantly more ulcers than conventional therapy alone after a 24-week period of treatment. Adapted from reference 42.

than 6 cm in diameter, in whom about a 65% reduction was found after 24 weeks of Daflon 500 mg treatment.

Recently a multicenter controlled, randomized study performed in 20 dermatologic clinics in the Czech and Slovak Republics (Roztocil and Stvrtinova, 2000, unpublished data) confirmed the benefit of Daflon 500 mg in the healing of venous leg ulcer in combination with compression therapy. The treatment period was 6 months and the dosage 2 tablets of Daflon 500 mg per day for 150 patients with CVI with venous ulceration, in combination with standard therapy (compression stockings together with local treatment). Eighty-two patients received Daflon 500 mg together with standard therapy and 68 patients standard therapy alone. The time to achieve complete healing was significantly shorter in the Daflon 500 mg group (137 days compared with the control group = 166 days [$p = 0.042$]), and a significantly larger number of patients had complete ulcer healing during the study with Daflon 500 mg (64.6%) in comparison with the control group (41.2%; $p = 0.04$). The mean area of the healed ulcer was significantly higher in the Daflon 500 mg group (77%), compared with the control group (69%; $p = 0.012$).

These studies showed that treatment with Daflon 500 mg at a daily dose of 2 tablets, in addition to conventional compression therapy, is of benefit in patients with venous leg ulcers, for it accelerates complete healing.

An explanation for the ability to speed ulcer healing comes from recent evidence that Daflon 500 mg treatment for 60 days decreases the immunoglobulin-like endothelial markers intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) involved in the adhesion of neutrophils and monocytes to the endothelium. Daflon 500 mg thus decreases leukocyte trapping and activation,[28,39,40] which may explain its anti-inflammatory effects.

Conclusion

The therapeutic strategies in the treatment of CVI include physical methods, such as elevation of the legs, compression therapy with bandages or elastic stockings, sclerotherapy, surgical correction of superficial or perforating vein incompetence where appropriate, and drug treatment.

With our present understanding of the pathophysiological events in CVI, it has become clear that there are both macrocirculatory and microcirculatory alterations to be targeted by therapy. Compression therapy and surgical procedures mainly are targeted towards the macrocirculation.

Daflon 500 mg, as a result of its comprehensive mode of action, addresses both the macrocirculation and the microcirculation at the same time. Daflon 500 mg is a venotropic drug that has demonstrated phlebotonic activities, lymphokinetic abilities, and modulation of inflammatory mediators and hemorheologic parameters in preclinical studies, as has been extensively reviewed.[44]

Studies performed on the leg ulcers have shown that treatment with Daflon 500 mg, in addition to conventional compression therapy, was of greater benefit compared with conventional compression therapy alone. This is an additional argument for the microcirculatory effects of Daflon 500 mg. The protective effect of Daflon 500 mg on the microcirculation may explain its ability to decrease edema, to limit skin disorders, and to accelerate the ulcer healing rate.

The efficacy of Daflon 500 mg thus embraces the entire range of pathophysiological mechanisms that characterize CVI, from the earliest stages of the disease to its more severe forms including venous leg ulcer.

There is clearly a role for Daflon 500 mg in the treatment of venous disease either prescribed alone in the early stages of the disease or as a part of the complex management of CVI associating compression treatments, sclerotherapy, and surgery if relevant, and pharmacologic treatments in more advanced stages.

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