Clinical Evaluation of the Efficacy and Safety of Calcium Dobesilate in Patients with Chronic Venous Insufficiency of the Lower Limbs

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Several venotonic drugs have been used in the treatment of chronic venous insufficiency (CVI) of the lower limbs, most of them from natural sources. Calcium dobesilate, from synthetic origin, has been shown to improve clinical symptoms of these venous conditions. Three hundred fifty-two patients with CVI in grades I and II of Widmer's classification were included from an open population between January 1999 and June 2000; patients received calcium dobesilate 500 mg every 8 hours for 9 weeks. A basal recording and recordings every 3 weeks were made of heaviness, pain, cramps, and paresthesias of the lower limbs with a severity scale, and edema was assessed by measurement of the circumference of ankles and calves. Two hundred eighty-six patients (81.3%) were women and 66 (18.7%) were men with a mean age of 45.7 ±14.1 years; 200 patients (56.8%) were grade I and 150 (42.6%) were grade II of Widmer's classification, and two patients had no classification, with a mean duration of symptoms of 6.5 ±7.4 years. All of the symptoms had a significant reduction from the first to the final visit of treatment; 70% of the patients complained of moderate to severe heaviness of the lower limbs at the beginning of the study, whereas 10% of the patients presented this symptom at the end of treatment. Likewise, 75%, 37%, and 41% of the patients, respectively, complained of moderate to severe pain, cramps, and paresthesias of the lower limbs at the beginning of the study, with a reduction in this prevalence to 6%, 2%, and 4%, respectively, at the end of treatment ($p<0.001$, Wilcoxon test). In regard to edema of ankles and calves, a significant reduction in circumferences was registered in both sites at the end of treatment; for instance, the mean circumference of the right ankle was reduced from 23.78 ±0.27 to 22.71 ±0.31 cm while the right calf had a reduction from 35.08 ±0.41 to 33.83 ±0.5 cm ($p<0.001$, paired t test). Side effects were registered in 17.9% of the patients. This trial shows that calcium dobesilate had significant efficacy in the improvement of all the symptoms in patients with CVI, achieving this effect with an acceptable safety profile.

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Introduction

Chronic venous insufficiency (CVI) of lower limbs is a frequent problem, seen most in women patients. This condition is observed in 15% to 20% of the general population.[1-3] Primary or secondary valvular insufficiency of perforating and superficial systems is considered a key factor for its pathogenesis, and other factors are involved such

as familial predisposition, alimentary habits, work activity, and a sedentary life style.[4,5] An increase of hydrostatic pressure is produced by the venous insufficiency in these systems, where a low pressure is normally observed.[6] This phenomenon affects microcirculation, inducing an increase of capillary permeability, with edema and damage due to compression of the lymphatic system.[7,8]

These alterations are clinically evident as varicose veins in superficial vessels and by symptoms such as heaviness, cramps, pain, dermatosis due to stasis, and edema of the lower limbs.[9]

Among the therapeutic approaches, the surgical procedure, which includes extensive ligature of both major and minor saphenous venous vessels, is reserved for highly symptomatic patients, those with superficial or deep thrombosis and/or those who are prone to develop skin ulcers[10-15]; other approaches are sclerotherapy[16-18] and external compressive therapy.[19,20] Moreover, the use of phlebotonic substances has been demonstrated to improve symptoms in these patients. Most of these substances are natural source products, such as ergotalkaloids, flavonoids, coumarinic- and heparinoid-like drugs, which lack significant scientific support with double-blind, placebo-controlled, and randomized clinical trials.[21,22]

Calcium dobesilate is a synthetic drug with effects at the capillary level. Among these effects are inhibition of vasoactive substances such as bradykinin and histamine and free radicals,[23-27] inhibition of those substances that induce mucopolysaccharide degradation, improvement of the network of basal membrane collagenoid substances, normalization of the resistance of capillary membranes, and reduction of capillary hyperpermeability.[28,29] Other effects of calcium dobesilate consists of hemorheologic actions, including platelet-antiaggregating action,[27,30-35] an increase in the flexibility and plasticity of erythrocytes,[36-39] a reduction of high-density plasma proteins such as fibrinogen,[35,40,41] and improvement of blood supply to the tissues. It also increases lymph circulation, which promotes reduction of edema.[22,42-44] An improvement of CVI symptoms has been noted in several multicenter, randomized, double-blind, placebo-controlled clinical trials.[45-51] The objective of this study was evaluation of the clinical efficacy of calcium dobesilate in the improvement of symptoms and assessment of the safety profile in an open population of patients with CVI.

Materials and Methods

Patients of either sex, with ages between 18 and 65 years and a diagnosis of chronic venous insufficiency of the lower limbs, grades I and II of Widmer's classification, were included.[49] Grade I includes dilatation of subcutaneous veins and Grade II includes hyper or hypopigmented areas, with or without dilatation of subcutaneous venous vessels. Patients had to present at least 2 of the following signs or symptoms: heaviness, cramps, pain, or dermatosis due to stasis and edema of the lower limbs, as a result of chronic venous insufficiency.

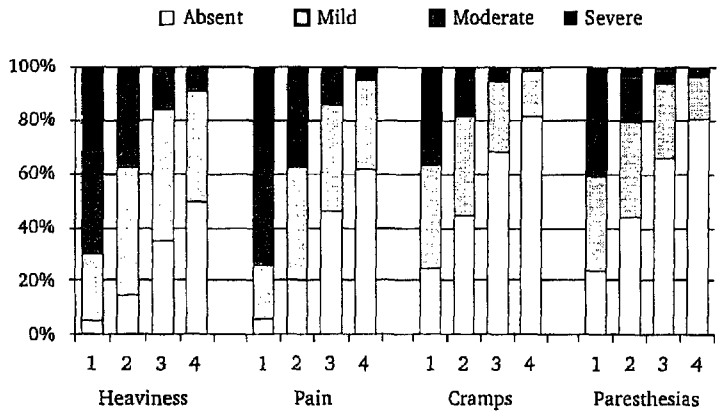

Figure 1. Evolution of severity of symptoms. Bars show the severity of symptoms in each of the 4 visits of the study. Symptoms were classified as absent, mild, moderate, and severe. Symptoms disappeared or were reduced during the study. $p < 0.001$, Wilcoxon test.

Patients with associated cardiovascular diseases (except those with controlled arterial hypertension) were excluded, as well as those receiving venous vasoactive drugs within 1 month before the beginning of the study, those with known hypersensitivity to calcium dobesilate, patients with varicose ulcers, patients treated with anticoagulating agents, pregnant women, and patients with thrombophlebitis or phlebothrombosis.

Patients received calcium dobesilate (Doxium®) 500 mg every 8 hours in an open design during 9 weeks. A clinical evaluation was performed at entry, including assessment of the Widmer's scale classification[49] and assessment of the severity of the following symptoms as qualitative parameters: heaviness, pain, and cramps and paresthesias of the lower limbs, by means of a severity scale with plus signs as follows: (+) mild, (++) moderate, (+++) severe, and (N) none. Furthermore, a measurement of the circumferences of the ankle and medium third of the calf in both legs was performed with a measuring tape, to evaluate edema. Body weight, blood pressure, and heart rate were additionally recorded.

Patients were subsequently evaluated every 3 weeks. In every visit the above-mentioned clinical parameters were assessed, in accordance with the severity scale and side effects were registered if present.

Qualitative parameters were analyzed with Wilcoxon and Friedman tests, while continuous events were analyzed with the paired Student's t test and analysis of variance for repetitive measurements.

Results

From January 1999 to June 2000, 352 patients from the general population who had a clinical profile of venous insufficiency of the lower limbs and who met the inclusion criteria were included. Sixty-nine physicians from the Republic of Mexico participated in the trial. The patient population included 286 (81.3%) women and 66 men (18.7%) who had a mean age of 45.7 ±14.1 years and who had a mean duration of symptoms of 6.52 ±7.43 years. Two hundred (56.8%) patients presented Grade I of venous insufficiency and 150 (42.6%) with Grade II in accordance to Widmer's scale classification.

The analysis of symptoms and edema, when compared to the basal registration and the assessments performed every 3 weeks, showed a significant reduction in severity of the condition. In 344 patients with heaviness of limbs it was severe in 108 (31%), moderate in 135 (39%), mild in 85 (25%), 8 patients had no severity score registered, and absent in 16 (5%) before the start of treatment, and these numbers improved significantly in the evaluation done after 21 days of treatment, with a lower amount of subjects in the severe (6%) and moderate (31%) scales of intensity and a higher amount of subjects in the mild (48%) and absent (14%) scales of intensity ($p < 0.001$, Wilcoxon test), and at the end of treatment there were 10% in the severe group, 41% in the mild group, and 49% without symptoms ($p < 0.001$) (Figure 1).

Seventy-five percent of the patients had moderate and severe pain initially, and this diminished after treatment to 6% ($p < 0.001$, Wilcoxon test). Similar effects were observed in the prevalence of moderate and severe cramps and paresthesias, with values changing from 37% and 41% to 2% and 4%, respectively ($p < 0.001$, Wilcoxon test). These last 2 symptoms initially had a high percentage of mild severity, and the symptoms were eradicated after treatment (Figure 1).

In regard to edema, there was a significant reduction in circumferences of ankles and calves of both legs, both in the first 21 days and at the end of treatment. Figure 2 shows results in right limbs, and similar changes were observed in left limbs. The mean circumference of the right ankle was reduced from 23.78 ±0.27 to 22.71 ±0.31 cm while the right calf had a reduction from 35.08 ±0.41 to 33.83 ±0.5 cm ($p < 0.001$, paired t test). A significant reduction in body weight was also observed at the end of treatment, 72.5 ±13.9 kg vs 71.1 ±13.3 kg ($p < 0.001$).

Ninety-two side effects were reported in 63 patients (17.9%) at some time during treatment; the most important included headache in 23 (6.5%), epigastralgia in 18 (5.1%), dizziness in 11 (3.1%), nausea in 5 (1.4%), and pyrosis in 10 (2.8%). Most of these vanished or were reduced at the end of treatment. Only 1 patient was withdrawn from the study because of severe gastritis.

Discussion

Chronic venous insufficiency of the lower limbs is an extraordinarily frequent health problem. Some investigators have estimated an incidence

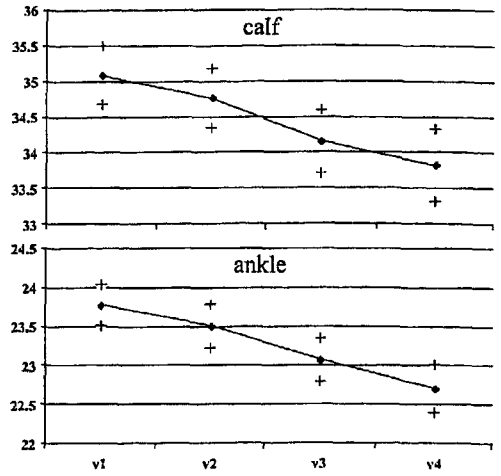

Figure 2. Evolution of circumferences of right calf and ankle (cm ± se); both presented a significant reduction after the initiation of treatment, $p < 0.001$, Student's t test, when values registered in visit 1 were compared with those of visits 2, 3, and 4.

of up to 86% in industrialized populations,[52] mainly in its mild to moderate clinical forms. The use of venotonic substances has been demonstrated to improve symptoms and performance of these patients.[21] Our study was designed to evaluate the efficacy and safety of calcium dobesilate in outpatients with mild to moderate CVI. We noted a significant improvement in subjective complaints such as edema and in reduction of body weight in these patients. Most of the patients showed a considerable reduction in or disappearance of symptoms. Reduction in the volume of edema represents a reduction in the volume of total body water, and this could explain, in addition to other factors, the significant reduction in body weight observed in the patients.

The incidence of side effects probably related to the drug (17.9%), is within the range of those reported by other investigators (0% to 27%),[46,47,49-51] the most important including headache, gastralgia, and dizziness.

Because this was an open noncontrolled study, some of the improvements can be attributed to a placebo effect and to the natural evolution of the disease. Nevertheless, it is also possible to consider that the clinical improvements were based on the actions of calcium dobesilate on the microcirculation of these patients with CVI, both at the capillary level, by inhibiting vasoactive substances and clearing oxygen free radicals, and at the hemorheologic level with its platelet-antiaggregating action, improvement of flexibility and plasticity of erythrocytes, reduction of blood hyperviscosity and, finally, improvement of the lymph circulation and consequent reduction of edema.[42-44]

Conclusion

This open study shows that calcium dobesilate had significant efficacy in improving symptoms in patients with chronic venous insufficiency of the lower limbs, while maintaining an acceptable safety profile. Calcium dobesilate is an interesting therapeutic option and can be an alternative to phytotherapy and to surgical procedures.

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