CALCIUM DOBESILATE – THE VASOACTIVE DRUG

INTRODUCTION

Calcium dobesilate is a vasoactive drug with presumed effects on endothelial integrity, capillary permeability and blood viscosity. It is often recommended for venous disorders, and also prescribed for diabetic retinopathy and other microvascular disorders.

MECHANISM OF ACTION

Calcium dobesilate has a comprehensive mode of action. It increases endothelial nitric oxide levels by enhancing the activity of nitric oxide synthase and decreasing capillary hyperpermeability. Calcium dobesilate shows anti-platelet and fibrinolytic activities by inhibiting platelet activation factor (PAF) and enhancing the release of tissue plasminogen activator (tPA), thereby improving the local blood flow to tissues, otherwise inhibited due to thrombosis. Calcium dobesilate also inhibits the two pathophysiological reactions in diabetes, viz. polyol pathway and glycation of proteins, due to its inhibitory effects on aldose reductase.

Calcium dobesilate acts on the endothelial layer and basement membrane of the capillaries. It reduces histamine and bradykinin-induced hyperpermeability. It increases red blood cell membrane flexibility and reduces capillary fragility. Calcium dobesilate can reduce the platelet aggregation stimulated by collagen and thrombin, but not by arachidonic acid.

Calcium dobesilate may also inhibit the formation of sorbitol, thus providing another possible mechanism for its usefulness in diabetic retinopathy.

Glucose inhibits the formation of both type I and type II collagen formation. Calcium dobesilate does not affect type I inhibition by glucose but accelerates type II collagen fibrillogenesis, a major structural component of the arterial wall.

Calcium dobesilate has angioprotective action by reducing the permeability and fragility of microvessels, which should restrict fluid extravasation into the cardiac interstitium. Its antiplatelet effect counteracts thrombosis and its reduction of plasma viscosity prevents stasis.

EFFECTS ON HEMORHEOLOGY AND MICROCIRCULATION

Studies suggest that calcium dobesilate has a favorable effect on hemorheological parameters. Since blood is not a liquid in the conventional sense but should rather be viewed as a suspension, a number of factors play a role in hemorheology which may give rise to various changes. Its formed elements give blood elastic properties, which are included in all viscosimetric techniques available to date.

A study by Koltringer et al tried to separate the apparent viscosity of whole blood, which includes both its elastic and viscous properties, into these two components and then to study them separately for alterations so as to assess the effects of the test compound more accurately. For this purpose, 50 patients with impaired cerebral or peripheral blood flow were studied. Of the randomly recruited patient sample, 33 subjects suffered from cerebrovascular insufficiency,
the remaining 17 suffered from impaired peripheral arterial blood flow stage IIa according to Fontaine. All patients were given 500 mg calcium dobesilate three times daily for a period of two weeks. They had not received any rheologically active medication. Before the start of the study and at 14 days, viscoelasticity of whole blood and plasma as well hematocrit and microcirculation were measured.

All viscosity and elasticity values fell in a highly significant manner, with plasma viscosity showing the greatest variation. In addition to the decrease in viscoelasticity, hematocrit also showed a highly significant decrease. Microcirculation was found to increase highly significantly. Fig.1 shows the percentage distribution of values before and after treatment.

These results fully justify the use of calcium dobesilate in hyperviscosity syndromes in the context of the treatment of impaired blood flow.

**EFFECT ON DIABETIC RETINOPATHY AND GLAUCOMA**

The pathogenic mechanisms of diabetic retinopathy (DR) are, as yet unknown. Several explanations have been offered (Fig. 2). One suggestion is that hyperglycemia leads to changes in biochemical processes that may result in anatomical and functional changes in the retinal vasculature. Platelet hyperaggregation normally follows the vascular lesions and is responsible for microthrombi and hypoxia. Hypoxia, in turn, causes vascular proliferation (increased vascular endothelial growth factor). Blood hyperviscosity is observed later in 30-40% of background retinopathy cases and is responsible for increased blood stasis and vascular occlusions. Proliferation and neovascularization, the final stages in DR, affect the microvessels (capillaries, venules and arterioles) and even the retinal veins and arteries, and it finally results in vitreous hemorrhage, retinal detachment and blindness.

According to Brunet et al., calcium dobesilate induced *in vitro* dose-dependent reduction of superoxide radicals generated by the xanthine/xanthine-oxidase couple and of the chemiluminescence induced by platelet activating factor (PAF) in human polymorphonuclear cells. An anti-PAF activity of calcium dobesilate was previously demonstrated in a dose-dependent manner, by inhibiting the production of PAF of an endothelial cell-line (EA926) stimulated *in vitro* by thrombin. Calcium dobesilate decreased lipid oxidation by oxygen-free radicals on human erythrocyte membranes and lowered the increase in cytosolic free calcium induced by hydrogen peroxide on cultured bovine arterial endothelial cells.
In 1977, Hudomel et al\textsuperscript{7} reported a statistically significant reduction of whole-blood viscosity in patients with diabetic retinopathy after treatment with the angioprotective agent calcium dobesilate, a finding which was reproduced by Barras and Gra\textsuperscript{8} in 1980, when they observed that a 3-month course of calcium dobesilate significantly lowered both whole-blood and plasma viscosity in this complication of diabetes.

Beyer et al\textsuperscript{9} found significant increases in intravascular retention of \textsuperscript{131}I-albumin, in total serum protein and in serum albumin in diabetics after a 6-month course of calcium dobesilate, effects which they described to reduction by calcium dobesilate, as a result of its vessel-sealing property of excessive transcapillary protein loss.

A study\textsuperscript{10} was conducted to observe effect of calcium dobesilate on the rheological status, the intraocular pressure (IOP), and the clinical condition in diabetic subjects with retinopathy and open-angle glaucoma. Fifty patients with diabetic retinopathy and open glaucoma were randomly allocated to treatment with 3 x 500 mg capsules of calcium dobesilate daily for 3 months or to 3 placebo capsules daily for the same period. A basic criterion for admission was the presence of blood hyperviscosity. The outstanding finding in this study is the significant reduction in hyperviscosity of whole blood, plasma and aqueous humor in patients with diabetic retinopathy and open-angle glaucoma treated with calcium dobesilate for 3 months, the reduction being accompanied by improvements in the state of the retina, in the visual acuity, and in the visual fields and by a fall in IOP.

**EFFECT IN CHRONIC VENOUS INSUFFICIENCY**

Chronic venous insufficiency (CVI) causes much discomfort and sick leave. It can result from alterations in the venous wall and valvular incompetence, leading to hemodynamic changes in the lower limbs. High pressures distend the veins and separate the valves, rendering them incapable of preventing the retrograde flow of blood. The resulting venous stasis and dilatation cause an increase in microcirculatory disorders. Patients with venous insufficiency often complain of a dull ache in the leg, and examination reveals increased leg circumference, edema, and the presence of other concomitant clinical symptoms (pain, cramps, swelling, heavy legs, paresthesia, ...
restless legs).\textsuperscript{11}

Calcium dobesilate exerts its therapeutic effect in microcirculatory disorders by reducing capillary permeability, inhibiting platelet aggregation and thrombus formation, lowering blood hyperviscosity, and increasing red cell flexibility. It also improves lymphatic drainage, which contributes to its anti-edematous effect. These properties have been confirmed in several double-blind and open-label, multicenter studies, particularly in diabetic retinopathy and in CVI.

A study\textsuperscript{11} was designed to evaluate the efficacy and safety of calcium dobesilate in a large population of ambulatory patients with overt chronic venous insufficiency, some of whom were unresponsive to other therapies. A large number of outpatients (n = 373; age range, 20 to 76 years) were treated for 28 days with 1.5 g calcium dobesilate per day. Efficacy was assessed by measuring the ankle and calf circumferences and by evaluating the evolution of each symptom frequency (pain, cramps, swelling, heavy legs, paresthesia, restless legs) before and after 14 and 28 days of treatment.

The results show that calcium dobesilate treatment produced significant clinical improvement in the CVI patients enrolled in this study. A significant reduction of ankle and calf edemas, corresponding to 4.4% and 2.8% of the respective initial circumferences and representing a reduced volume of 0.13 L, was noted in more than 82% of patients at the outcome compared with baseline conditions. These objective measures resulted in indisputable physical improvement. Symptoms such as pain, cramps, swelling, heavy legs, and paresthesia were markedly improved as well (see Figs. 3,4).

Ciapponi et al\textsuperscript{12} report a meta-analysis of the effectiveness and safety of calcium dobesilate in CVI. In ten RCTs (778 patients), calcium dobesilate was compared with placebo in the treatment of CVI. Calcium dobesilate significantly improved night cramps and dis-

Fig. 3: Evolution of ankle and calf perimeters after 14 (visit 1) and 28 (visit 2) days of calcium dobesilate therapy compared with entry conditions.

Fig. 4: Mean symptom frequency as a function of time of treatment evaluated as follows: 0 = none, 1 = once a week, 2 = twice or more a week.
comfort nearly twice as well as placebo.

**CONCLUSION**

Going by the aforesaid evidence, calcium dobesilate has been proved to be an ideal drug for the treatment of diabetic retinopathy and various venous and microvascular disorders.

**REFERENCES**

Perioperative Treatment of Patients with Varicose Veins Using Calcium Dobesilate

Altogether 120 patients with medium to serious forms of varicosities were examined perioperatively after having been divided into 3 groups. Groups I and II were administered perioperatively a daily dosage of 1000 mg (2 x 1 capsule) of calcium dobesilate during 8 weeks - 2 weeks preoperatively and 6 weeks postoperatively. Group III was used for control purposes. The following were valued as parameters of comparison: kind and seriousness of perioperative trouble, alteration of peripheral edemas, results of plethysmographic examinations as well as light-reflex-rheography examinations and the post-operative healing-process. Groups I and II showed a significant (p less than 0.05) reduction of the peripheral edemas already in the preoperative state and postoperatively, the patients had less trouble and a quicker healing-process was observed compared with group III.


Calcium Dobesilate Lowers the Blood Pressure in Mild to Moderate Midtrimester Hypertension: A Pilot Study

To test the effects of calcium dobesilate in pregnancies complicated with pregnancy-induced hypertension or mild/moderate pre-eclampsia a double-blind, placebo-controlled pilot study was carried out. Primigravida patients (gestational age ≤34 weeks) daily took 2 g calcium dobesilate or placebo until delivery. Twelve patients received placebo for 53 days, and 11 patients took the drug for 57 days on average. At the start of the study 2 patients in the placebo group (PG) and 8 in the calcium dobesilate group (DG) had pre-eclampsia. The mean arterial pressure (mean ± SD) significantly decreased from 118 ± 7 to 99 ± 9 mmHg in the DG (p = 0.003), while in the PG it had slightly increased by the end of the study. Proteinuria was higher in the DG at the start but not at the end; however, significant changes of this parameter were detected in neither of the groups throughout the study. Fibronectin decreased significantly in both groups but it was more pronounced in the DG (23.8 vs. 9.4%). Changes of platelet count, plasma and blood viscosity, and erythrocyte deformability were favorable in the DG but in the PG these parameters had deteriorated although the alterations were not significant. No marked differences were found between the two groups regarding fetal well-being, courses of deliveries, and the neonatal period. Neither maternal nor fetal/neonatal side effects were noticed. It seems that calcium dobesilate favorably influences the blood pressure and consequently decreases the requirement for medication and hospitalization in cases of mild to moderate midtrimester hypertension.

DOBEST
(CALCIUM DOBESILATE)

Helps Patients Do their BEST