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Calcium dobesilate in Dermatology

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Abstract
Phlebotonics are a heterogeneous class of drugs mainly used to treat chronic venous insufficiency and haemorrhoids. Most of these drugs are natural products extracted from plants (flavonoids, sapsonides, etc), but synthetic products are also used (calcium dobesilate). Calcium dobesilate is a synthetic venoactive drug thought to have antioxidant properties, reduce capillary permeability, increase venous tone and reduce inflammation. Calcium dobesilate (Cd) has been used successfully in chronic venous insufficiency, venous ulcers and stasis dermatitis, acute attacks of hemorrhoidal disease, diabetic retinopathy, gestational hypertension and myocardial infarction. Its antioxidant and angioprotective functions are responsible for these effects. It is safe, cheap and easily available therapeutic option for various disorders with gastrointestinal disturbances being the most common adverse effects.
Keyword: *Phlebotonics, Phlebotropic drugs, Venoactive drugs, Calcium dobesilate (dobesilic acid, Cd), Chronic venous disease (CVD).*

Introduction

Venoactive drugs/ Phlebotropic drugs/ Phlebotonics: Venoactive drugs are a heterogeneous group of drugs mainly derived from plant extracts. Some have been produced by chemical synthesis. Their actions are similar to those of compression therapy, they reduce inflammation of the venous wall, oedema formation, the development of skin changes, and protect endothelial cells from contraction. Relief of symptoms is the main objective of pharmacological treatment of chronic venous disease (CVD), and strong evidence exists for an objective effect on oedema and venous symptoms. Data indicate that the use of venoactive drugs is both safe and economic, with digestive side effects the main notable adverse outcomes.[1] The main phlebotropic drugs are summarized in *Table I.*

Pathophysiological targets of phlebotropic drugs

Based on the mode of action of phlebotropic drugs depending on the pathophysiological mechanisms that they aim to treat the mechanisms can be differentiated into the following:

- those that are identified before microcirculatory disorders occur,

consisting mainly of alterations in the venous wall; and

- those consisting of microcirculatory disorders.[2]

Pharmacological action of phlebotropic drugs on these different targets: Remacle's team has demonstrated the ability of phlebotropic drugs to inhibit the release of mediators of inflammation in endothelial cells placed under conditions of hypoxia (Figure 1).

Table I: Summary of Venoactive drugs

Group	Substance	Origin Evidence	Grade*†	Trials and meta-analyses
Benzopyrones				
Alphabenzopyrones	Coumarin Melilot (*Melilotus officinalis* L.)	Woodruff (*Asperula odorata* L.)	Grade C‡	2
Gamma-benzopyrones (flavonoids)				
Flavones	Diosmin *Citrus spp.*	*Sophora japonica* L.	Grade C	1
	MPFF (micronised purified flavonoid fraction)	*Rutaceae aurantiae*	Grade A	1
	Rutin and rutosides, O-(β-hydroxyethyl)-rutosides(troxerutin, HR)	*Sophora japonica* L. *Eucalyptus spp.* *Fagopyrum esculentum* Moench	Grade A	4
Flavonols Quercetin glucoside,	kaempferol, glucoside, quercetin glucuronide	Red-vine-leaf extract(*Vitis vinifera*)	-	-
Flavanes and flavanones	Hesperetin, hesperidin, catechin, etc.	Various plants -		-
	Anthocyanosides	Blueberry extracts (*Vaccinium myrtillys* L.), red-vine-leaf extract (*Vitis vinifera*)	-	-
	Proanthocyanidines(oligomers)	Grape pips (*Vitis vinifera*)	Grade C 1	3
Saponins				
	Escin Horse	chestnut seed (*Aesculus hippocastanum* L.)	Grade B	3
	Ruscus extract	Butcher's broom (*Ruscus aculeatus* L.)	Grade B	1
Other plant extracts				
	Centella asiatica extracts	*Centella asiatica*	-	-
	Ginkgo biloba extracts	*Ginkgo biloba* L.	Grade C	-
Synthetic products				
	Calcium dobesilate 2	Synthesis	Grade A	2
	Benzarone	Synthesis	-	-
	Naftazone	Synthesis - -	Grade C	1
Animal-derived extracts				
	Mesoglycan	Polysaccharides from different animal tissues	-	-

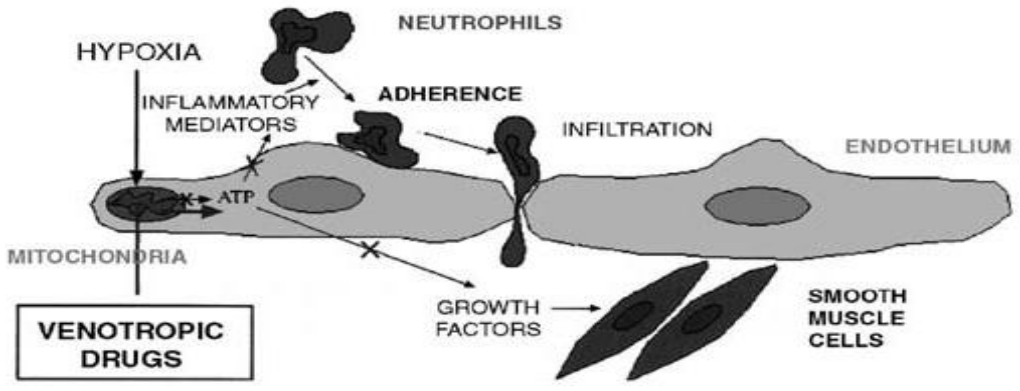

Figure 1. Possible mechanism of protection of endothelial cell by phlebotropic drugs

Table II. Pharmacological targets of phlebotropic drugs.

Effects		Products
1	Analgesic, antiedema and capillary protection effects	all products
2	Venous tone	all products
3	Lymphotrophic effects	*Ruscus, coumarin, micronized purified flavonoid fraction*
4	Improvement of red blood cell rheology	*micronized purified flavonoid fraction, troxerutin, rutin*
5	Profibrinolytic action	*micronized purified flavonoid fraction, troxerutin, diosmins*
6	Anti-inflammatory action	*micronized purified flavonoid fraction, Gingko biloba, diosmins*
7	Decreased adhesive properties of neutrophils and monocytes	*micronized purified flavonoid fraction*
8	Protective effect on the venous valve	*micronized purified flavonoid fraction*
9	Protective effect on the venous wall	
	1: inhibition of lysosomal enzymes	*melitot extract, rutins, pycnogenols*
	2: protection of fibrous proteins (collagen)	*procyanidolic oligomers*
	3: anti–free radical properties	*micronized purified flavonoid fraction, Gingko biloba*
	4: normalization of the synthesis of prostaglandin E2	*micronized purified flavonoid fraction*
	5: improvement of circulation in the vasa vasorum	*troxerutin*

Calcium dobesilate

Calcium dobesilate (dobesilic acid, Cd) is a synthetic product in crystalline powder form. It is absorbed from the intestine and attains a peak plasma concentration (8 mcg/ml) within 6 hours of oral administration. It is distributed throughout the body except for the brain. Seventy five percent of the unchanged drug is excreted in the urine and the remaining 25% in feces in 24 hours.

The mode of action:

a) Dobesilate ion induces the synthesis and release of nitric oxide (NO) in endothelial cell cultures. This causes relaxation of the vessels, closure of the gaps and reduced capillary hyper-permeability. Furthermore, NO modulates leukocyte adhesion, an early factor in the development of tissue inflammation and protects against endothelial cell injury.

b) Cd induces *in vitro a* dose-dependant reduction of super oxide radicals generated by the xanthine/xanthine-oxidase couple and the chemiluminiscence induced by platelet-activating factor (PAF) in human polymorphonuclear cells. It also preserves vascular endothelial function by acting directly as an antioxidant to protect lipid from peroxidation.

c) Cd inhibits smooth muscle cell proliferation *in vitro* and *in vivo*, thus demonstrating action on arterial macrocirculation.[3]

Dosage and routes: it is given orally in usual doses of 0.5 to 1.5 g daily in divided, rectally for haemorrhoids and as topical preparation for various dermatological disordes.

Adverse effects: Gastrointestinal disturbances are the most common adverse effects Hypersensitivity reactions, agranulocytosis, fever and arthralgias can occur rarely.[4]

Dermatological Uses

Chronic venous efficiency(CVI)

Calcium dobesilate improves capillary and vein wall function and integrity, reduces blood and fluid extravasation and oedema formation. It acts on blood components to reduce erythrocyte fragility and inhibit platelet aggregation. This leads to reduced plasma viscosity and thrombosis formation in the microcirculation. It improves capture of fluid and macromolecules from the extracellular space thereby accelerating lymph flow which acts to normalize lymph physiology and improve symptoms. 1.5 g of calcium dobesilate per day for at least 4 weeks achieves significant improvements in the symptoms of CVI.[1]

Pigmented Purpuric Dermatosis

Based upon the promising results in trials, Cd is being visualized as the first line therapy in PPD in a dose of 500 mg twice daily for two initial weeks and then 500 mg once daily for a total period of three months. The vasoprotective, antioxidant, anti-inflammatory and antiproliferative effects of Cd has the potential to prevent the pathological changes seen in PPD. Cd has its best effect only in the active phase of disease because no significant improvement is noticed later than two months of

therapy and new lesions stops appearing after only two weeks of treatment.[3]

Rosacea

Local inhibition of angiogenic factors by dobesilate may prevent skin angiogenesis and inflammation in rosacea and other angiogenesis-dependent skin diseases in which a dense network of new vessels is produced and inflammatory cells are present. It may also play a role in the reduction of inflammation by regulating the synthesis of inflammatory molecules in rosacea. Furthermore, since FGF acts as survival factor for many cell types including endothelial cells it is likely that inhibiting FGF function by dobesilate represents a biological relevant mean of producing apoptotic endothelium in rosacea vessels. Cd suspension 2.5% in the treatment of rosacea, provides a new and attractive therapeutic option for the treatment of this disease.[5]

Plaque Psoriasis

Topical Cd is a very useful nonatrophogenic, nonirritating and FDA approved drug for the treatment of plaque psoriasis. Potassium dobesilate cream 5% is effective for the treatment of chronic-type plaque psoriasis. Cd acts by reducing capillary hyperpermeability and induces substantial and rapid clinical improvement in erythema, desquamation, induration and overall severity. In addition to its antiproliferative and proapoptotic functions, dobesilate may also be effective by abolishing T cell activities in psoriasis.[6]

Calcium Dobesilate in BCC

The agents promoting apoptosis are considered useful candidates for nonsurgical treatment of tumors. Because epidermal skin cancers overexpress FGF, blocking FGF signaling may be a therapeutic strategy for BCC treatment. Cd 2.5% in a suspension formulation, applied twice daily) for 4 weeks induces progressive decrease in tumor size after 4 weeks there was nearly complete clinical resolution of the disease is seen(a case report).[7]

Non-Dermatological Uses

Calcium dobesilate in diabetic retinopathy

Administration of the CaD tablets (500 mg daily) for 3 months in the patients with diabetic retinopathy may reduce the serum levels of endothelin-1 and hsCRP. This might imply amelioration of the endothelial function and inflammatory status following CaD therapy in these patients.[8]

hemorrhoids

Oral Calcium dobesilate capsule 500 mg given in the dosage of two capsule twice a day for one week followed by one capsule for once a day for 5 weeks as well as topical calcium dobesilate ointment (0.5%w/w) applied twice a day before and after defecation supplemented with diet and bowel habits. It provides an effective, fast, and safe symptomatic relief from acute symptoms of hemorrhoidal disease along with significant improvement in anoscopically observed inflammation.[9]

glioma

Fibroblast growth factors (FGFs) and their receptors, regularly expressed at high levels in gliomas, are further upregulated during the transition of the tumor from low- to high-grade malignancy, and are essential for glioma progression. FGFs induce upregulation of the mitogen-activated protein kinase (MAPK) signaling cascade in cultured glioma cells, which suggests that MAPK pathway participates in the FGF-dependent glioma development. Recently, it has been shown that dobesilate, an inhibitor of FGF mitogenic activity, shows antiproliferative and proapoptotic activities in glioma cell cultures.[10]

Other uses

Gestational hypertension and myocardial infarction are other indications of Cd use.[3]

Decreased serum levels of total cholesterol, triglycerides, and AST following the Cd administration (500 mg/d for 3 months) were observed by Benarroch et al. In contrast, Beyer et al. reported unchanged levels of both cholesterol and triglycerides in diabetic patients 6 months after treatment with CaD (750 mg/d).[8]

Conclusion

Calcium dobesilate is an effective, safe, cheap and easily available therapeutic option for various disorders. It has a unique multi-target mode of action and preserves microvascular integrity and improves microvascular circulation. Dobesilate reduces leg oedema and improves the symptoms of objectively diagnosed CVI, independent of the concomitant usage of compression stockings. It is well tolerated with a low incidence of minor reversible digestive disorders. The efficient and safe benefits of Calcium dobesilate provides a new and attractive therapeutic option in the treatment of various disorders.

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