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Three Treatments for Chronic Venous Insufficiency: Escin, Hydroxyethylrutoside, and Daflon

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ABSTRACT

Escin, hydroxyethylrutoside (HR), and Daflon have been shown to be safe and effective for the treatment of chronic venous insufficiency (CVI). They seem to work differently than compression therapy, suggesting that they would usefully augment this therapy. All three phlebotonics attenuate the drop in adenosine triphosphate in venous endothelial cells during hypoxia. This attenuates (1) the inflammation response, (2) the attraction of neutrophils, (3) damage to the veins, and (4) the release of growth factors. These factors otherwise would perpetuate venous insufficiency and contribute to varicose veins. Additional independent effects that would be useful for the treatment of CVI are that they reduce permeability and fragility; HR, Daflon, and perhaps escin increase venous tone; escin inhibits hyaluronidase; Daflon and probably HR are attracted to the veins. With regard to similarity, no differences in effect have been established among these phlebotonics.

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Introduction

Chronic venous insufficiency (CVI) is a serious problem. Ruckley[1] estimates that approximately 5% of the adult population suffers from CVI. In addition to undesirable symptoms—edema, a sensation of heaviness, varicose veins—CVI can lead to the serious problem of leg ulcers.

The standard treatment for CVI in the United States is compression therapy. However, in Europe, several phlebotonics are also used to treat CVI. This article considers three phlebotonics that currently are advocated for use in treating CVI: escin, hydroxyethylrutoside (HR), and Daflon. The first section of this article addresses their safety and effectiveness. The second section considers why they might be useful in treating CVI and their similarity.

Effectiveness and Safety

Escin

Escin is the active ingredient in the extract of horse chestnut *(Aesculus hippocastanum)*. The most optimistic (though not experimental) report is by Greeske,[2] who observed escin's outcome in more than 5,000 patients with CVI. Greeske looked at a variety of symptoms: pain, tiredness, tension, swelling, and itching in the leg. All of these "improved markedly or disappeared completely." Experimentally, eight controlled studies have all found that escin reduces the symptoms of CVI, including a reduction in swelling, leg pain, itching, and the feeling of fatigue and tenseness.[3] Escin also reduced capillary filtration rate by 22%.[4] Escin was as effective as compression therapy in a 12-week trial, with both producing about a 25% reduction in swelling.[5]

Hydroxyethylrutoside

The semisynthetic flavonoid HR (oxerutin) is a standardized mixture of benzopyrone derivatives produced by substituting hydroxyethyl groups in the naturally occurring flavonol rutin.[6] A good review of it is by Wadworth.[6] The most common substance in HR is troxerutin (38%), and troxerutin was once used by itself for treating CVI. However, HR is more effective than just troxerutin.[7]

A metaanalysis by Poynard[8] showed that HR improves the symptoms of CVI, including pain, cramps, restless legs, swelling, and tired legs. HR also increases the oxygen in the blood by 30%[9] and the oxygen in the skin of patients with leg ulcers.[10] Poynard's metaanalysis suggests that the effect of HR is not large—HR caused a complete disappearance of a symptom only 11% to 24% more often than a placebo. However, the complete disappearance of a symptom, while a useful measure for a metaanalysis, is not a sensitive measure of improvement.

Even the two least favorable studies according to Poynard's measure[11,12] reported a beneficial effect of HR. MacLennan et al[12] in fact reported a substantial effect for HR—for MacLennan's index of overall effect, which did not include the measures considered in Poynard's metaanalysis, HR decreased symptoms 60%, compared to 32% in the control group. This comparison is compromised by the fact that the HR group started with more severe symptoms, but the fact remains that even the studies least optimistic about HR support its effectiveness.

Unkauf et al[13] compared HR plus compression therapy with compression therapy alone. After 12 weeks of treatment, the compression therapy reduced swelling by 33 mL, whereas the compression therapy plus HR reduced swelling by 64 mL. One study[14] found that HR was more effective than escin, but another study[15] found that escin was more effective than HR. Two other studies[16,17] found no difference. Pittler[3] concluded that HR and escin were about equally as effective.

Daflon

Daflon is a mixture of 90% diosmin and 10% hesperidin, two flavonoids. Diosmin can be found in many citrus fruits, and hesperidin is found in the rind of several citrus fruits. They are "micronized" to increase absorption.[18] The sugar moiety of diosmin is cleaved during digestion and it is absorbed in its aglycone form, as diosmetin.[19]

A 2-month treatment with Daflon improved functional discomfort, the sensation of heaviness, the sensation of weakness, and a burning sensation.[20] For example, there was an 80% improvement in functional comfort for Daflon, as opposed to only 38% for a placebo. There was also a re-

duction in swelling of the ankle. A clinician made the following evaluation: For Daflon, the effect was very good in 44% of the cases, of some benefit in 33% of the cases, and of no benefit in 22% of the cases. The placebo was rated as very good in 6% of the cases, as of some benefit in 44% of the cases, and of no benefit in 50% of the cases. Daflon also improves blood velocity in the skin microcirculation.[21]

Daflon works better than diosmin alone.[22] For example, 80% of the subjects with venous insufficiency were happy with diosmin, but 95% were happy with Daflon. The clinician's ratings, for a 2-month treatment: 79% good and 21% useful for Daflon; 51% good, 29% useful, and 20% no benefit for diosmin. This advantage could be because of the hesperidin or the micronization.

Slow But Continued Effectiveness

Escin

As noted, one study found that escin and compression therapy produced equivalent reductions in swelling by the end of 12 weeks.[5] However, the compression therapy and escin apparently worked at different speeds. By the end of 4 weeks, the compression therapy had reduced swelling more than escin. However, the compression therapy produced no further observable improvement, while the escin further reduced swelling over the course of the next 8 weeks, so that it was equivalent to compression therapy by week 12. Measures of the quality of life and disability followed the same course as the swelling—immediate improvement from the compression therapy, with the escin reaching equivalence by week 12.[23]

Thus, it seems that the effect of escin has a different time course from that of compression therapy and that escin produces a slow but increasing effect. Two studies[24,25] did find improvement for escin after 2 weeks. In another study, escin continued in effectiveness after treatment stopped.[14]

HR

In one study,[7] HR produced no observable sign of improvement after just 2 weeks. Signs of improvement appeared by 4 weeks and were maximal at 8 weeks. There was no sign of improvement from 8 weeks to 12 weeks. When treatment was discontinued, patients receiving troxerutin alone returned to their original level of edema, whereas the improvement produced by HR persisted. In another study, HR continued in effectiveness after treatment stopped.[14] Casley-Smith[26] tested the effects of HR on lymphedema and elephantiasis. Six months of treatment was required to produce a 50% reduction in edema. In the study comparing HR plus compression therapy with compression therapy alone,[13] there was a 6-week period following the experiment in which the subjects received no treatment. The subjects who had used compression therapy plus HR continued to improve, whereas the subjects with compression therapy alone did not.

Daflon

The improved blood velocity in the skin microcirculation found with Daflon was maintained during 2 weeks of no treatment.[21]

Summary

It seems to take at least 2 weeks before escin and HR produce observable signs of improvement. All three phlebotonics have effects that persist beyond treatment.

Safety

Escin

According to Pittler,[3] the reported potential adverse effects of escin are dizziness, nausea, headache, and itching. The frequency of these ranges from 0.9% to 3% across experiments, and several studies have found no more adverse effects with escin than with placebo. Typical comments are "The tested preparations were well tolerated."[27] In the 1992 study by Diehm et al,[27] the compliance rate was 98% for escin and 90% for compression therapy, suggesting that the patients preferred escin over compression therapy.

No signs were found that escin produced DNA damage or was carcinogenic,[28] and escin causes no kidney damage at the dosages usually taken.[29]

HR

HR "has generally been well tolerated by patients."[14] Reported effects are infrequent and mild, the most common being gastrointestinal disorders, headache, dizziness, and itching. In most studies, the placebo group reports as many adverse effects as does the patients treated with HR. For example, MacLennan et al[12] tested older people, some for more than 6 months. Looking at a variety of potential adverse effects, there was no difference between the subjects taking HR and the subjects taking the placebo. HR does not interact with warfarin.[30]

Daflon

Daflon appears to be as well tolerated as escin and HR—no more adverse effects are reported for Daflon than for a placebo.[31] In the rat, 0.003% of the administered dose has been found in each fetus and 1% in breast milk. Daflon has no observable mutagenic effect or effect on reproduction.[31] There is no untoward accumulation in any organ.[31] Neither diosmin or diosmetin produces liver damage,[32] and Daflon had no observable effect on the fetus when taken by women near the end of pregnancy.[33]

Physiological Effects

This report considers four factors that might contribute to effective treatment of CVI: protecting endothelial cells from the effects of hypoxia, decreasing permeability and fragility of the veins, increasing venous tone, and being attracted to the venous endothelium.

Protection from Hypoxia

The idea that cells might suffer hypoxia in chronic venous insufficiency is old and debatable,[34] but evidence suggests that hypoxia could account for many of the interrelated problems of venous insufficiency, including the continuation of the problem.[35,36] The most likely candidates for hypoxia seem to be the endothelial cells.[14,37] Suppose that for some reason, the endothelial cells do not receive enough oxygen. Numerous in vitro studies of venous endothelial cells or human umbilical vein endothelium by Michiels and colleagues[38] have found that hypoxia causes a decrease in adenose triphosphate (ATP). One effect of the decreased ATP is the activation of phospholipase A2, leading to the release of prostaglandins.[38] The release of prostaglandins leads to an inflammation response, including edema. This edema presumably slows the flow of blood and lymph through the region, increasing hypoxia.

The decreased ATP also triggers the release of platelet-activating factor.[39] Platelet-activating factor and prostaglandins activate neutrophils and increase their adherence to the endothelial cells.[39-41] The platelet-activating factor and the attraction of neutrophils to the vein walls could obstruct blood flow in the veins, reducing blood flow and increasing hypoxia.

Neutrophils release elastase, among other caustic substances. Elastase degrades elastin, which is the elastic portion of the smooth muscles in the veins. Elastase also causes the release of basic fibroblast growth factor.[42] More generally, a shortage of ATP leads to the release of several growth factors for smooth muscle cells.[43] Any enlargement of the veins presumably would further increase venous insufficiency, and the combination of degradation and growth might contribute to varicose veins.

Thus, venous insufficiency leads to more venous insufficiency. If the problem initially causing the venous insufficiency is still present, it needs to be addressed. However, over and above that, if hypoxia leads to the continuation of chronic venous insufficiency, effective treatment for CVI presumably should include something to attenuate the undesirable consequences of hypoxia.

Treating endothelial cells with escin attenuates the decrease in ATP caused by hypoxia.[36-44] Further steps of the cascade are then attenuated—the escin-treated cells have less activation of phospholipase A2 and less adherence for neutrophils.[36,44]

HR also protects against cell death during hypoxia.[45] More specifically, it conserves ATP during hypoxia, with again further steps in the cascade being attenuated—the activation of phospholipase A2 and the attraction and adhesiveness of neutrophils.[46,47]

Diosmin also protects the cells' ATP during hypoxia.[48] With regard to further steps in the cascade, Daflon has been found to reduce prostaglandin E_2 (PGE_2), $PGF_{2\alpha}$, and thromboxane A_2 (TXA_2).[49,50] It also decreases the tendency of leukocytes to adhere to the endothelium.[51]

Thus, all three phlebotonics serve to conserve ATP during oxygen shortage. This could at least partially explain their effectiveness. Michiels et al[48] offer no explanation of why these phlebotonics conserve ATP, except to rule out the obvious explanation of early glycolysis. Glycolysis does increase when cells are deprived of oxygen, but an investigation of Ginkgo Biloba, which also conserves ATP during hypoxia, found that it slowed the onset of glycolysis.[52]

Decreasing Permeability and Fragility

Escin attenuates permeability in both the veins and capillaries,[53] when permeability is induced. Under normal conditions, escin has no effect on permeability.[53] Escin has also reduced edema.[53] Numerous studies have shown that HR reduces permeability,[14] and Daflon also reduces permeability.[54]

Kreysel et al[55] theorize that the same factors that increase permeability also increase the fragility of the endothelial cells. The notion is that permeability is achieved by increasing the gaps between cells, which would increase fragility. Kreysel looked at three enzymes associated with the destruction of the proteoglycans holding endothelial cells together: arylsulfatase, β-glucuronidase, and N-Ac-hexosaminidase. These enzymes were more prevalent in patients with varicose veins. For example, β-glucuronidase was 70% more active in patients with varicose veins than in control subjects. (Hayer et al[56] reported a correlation between the severity of varicosis and β-glucuronidase but not arylsulfatase; Stvrtinova[57] reviews other studies showing a correlation between varicose veins and a variety of lysosomal enzymes.)

Treatments with escin for 12 days reduced the activity of these enzymes.[55] The effect was not immediate, appearing after 2 days and increasing up to the 12th day. Three additional days of no treatment did not cause the activity of these enzymes to rise, suggesting that escin has an effect beyond the treatment period. Daflon also decreases the fragility of the capillaries.[58]

During hypoxia, these three phlebotonics would decrease permeability via their conservation of ATP. However, the above-cited demonstrations of a reduction in permeability seem to be unrelated to hypoxia. Therefore, it seems that the ability to decrease permeability is in addition to the ability to conserve ATP during hypoxia.

Escin also inhibits hyaluronidase.[59] Hyaluronidase is the enzyme that makes hyaluron, which also increases permeability and fragility. Hyaluronidase also has been found to facilitate growth of the smooth muscle cells.[60]

Increasing Venous Tone

Escin has been shown to increase the venous tone of in vitro human veins.[53,61] Guillaume[53] found that it also improved contraction of the venous valves. In terms of the maximum amount of contraction that could be reached, escin was similar to serotonin and dihydroergotamine, greater than acetylcholine or vasopressin, and not as strong as norepinephrine or histamine.[61] The effect of escin was maintained an hour after it was removed, suggesting that escin prevents the breakdown of noradrenaline. An in vivo effect of escin was not detected, however.[4,24] It is not clear whether this is because the effect could not be detected or because escin behaves differently in vitro.

Daflon immediately increases venous tone in healthy subjects, and it increases venous tone in patients with CVI.[20,62] Boudet[63] concluded that diosmin inhibited the activity of catechol-O-methyltransferase and enhanced catecholamine release. HR also increases venous tone in patients with CVI.[64]

Attraction to the Veins

Attraction to the veins would be a very desirable property in a substance intended to treat chronic venous insufficiency; attraction to the venous en-

dothelium would be especially desirable if hypoxia of the endothelium is a problem. Diosmin, the primary component of Daflon, is attracted to the veins.[65] When HR is given intravenously, it is preferentially taken up by the endothelial cells in the wall of the veins.[66,67] When HR is taken orally, it does not show up on the endothelial wall. Neumann et al[67] hypothesized that this is because it is metabolized (by losing its glycoside). This aglycone of HR was not detectable with Neumann's method of locating HR. Therefore, it is not known if metabolized HR is attracted to the vein walls, though this seems plausible.

Conclusions

Implications for Treatment

These three phlebotonics seem to be safe and effective treatments for CVI. They might sometimes completely resolve a symptom of CVI, but the usual outcome appears to be an improvement in CVI rather than a cure (at least over the usual time course of an experiment). This seems reasonable given that they apparently do not address the possible initiating factor for CVI.

There is no evidence to suggest that they are more or less effective than compression therapy. Therefore, they could be used as a replacement for compression therapy. However, they seem to work differently than compression therapy. Therefore, the combination of compression therapy and one of these phlebotonics probably would be more effective than one of these phlebotonics alone.

Important information about dosage seems to be lacking. There are fairly standardized doses of these substances. Escin is typically administered at 100 to 150 mg a day[3]; a typical dose of HR is 900 to 1,200 mg per day[14]; and the typical dose for Daflon is 1,000 mg a day. At these doses, essentially no adverse effects occur. The points are that (1) larger doses might be more effective, and (2) there seems to be no published knowledge concerning the dose at which significant adverse effects are observed. Larger doses might be well tolerated. For example, oxerutin's recommended dose for the treatment of lymphedema is 3,000 mg,[14] which is about three times the level used to treat CVI, suggesting possibly a considerable margin of error in producing adverse effects.

Similarity

Currently, there is no firm basis for differentiating these three phlebotonics; no effect was known to occur for one phlebotonic and not for another. However, a number of effects were known for one or two phlebotonics and not for the others. Future research should investigate whether these phlebotonics have the same effects. Any differences might provide some basis for choosing between them in treatment.

If these phlebotonics have the same effects, the confluence of desirable effects would be striking—substances that conserve ATP during hypoxia, reduce permeability, constrict the veins, and are attracted to the veins. Even if the three phlebotonics are not identical, their similarity still might deserve explanation. Perhaps they are analogs of a naturally occurring substance that protects veins during hypoxia.

As noted, HR and diosmin are broken down to their aglycone and digested as such. Future in vitro and pharmacologic research should either test the aglycone or explain why there is no problem testing the glycoside. Escin and hesperidin are also glycosides; I could not find any information about their fate during digestion.

What Causes Chronic Venous Insufficiency?

Thrombosis, varicose veins, and ulcers are clearly defined problems, their names describing the definitive factor. CVI, in contrast, is unclear. The name does not indicate what about the veins is insufficient, and the term *chronic* seems extraneous—no one differentiates CVI from nonchronic possibilities. Definitions of CVI vary. For example, CVI has been defined in terms of valvular incompetence,[68] ambulatory venous hypertension,[34] or even varicose veins,[34] all of which are different from the traditional symptoms of CVI such as swelling and a sensation of heaviness.

Some explanations of CVI are purely "hydraulic." For example, Norgren[34] writes that "continuous venous hypertension may distend the veins and prevent the valves from closing efficiently, thereby causing a reflux to occur, which in turn increases the distension of the veins." From the hydraulic point of view, compression stockings are a logical therapy. These three phle-

botonics have hydraulic effects, such as increasing venous tone and decreasing permeability, and these hydraulic effects might be the basis for their effectiveness.

However, biochemical factors also contribute to CVI. From a biochemical perspective, these three phlebotonics make sense—they influence prostaglandins, the activation and adherence of neutrophils, growth factors, and hyaluronidase. The fact that these three effective phlebotonics attenuate the problems of hypoxia suggests that hypoxia might be a self-perpetuating factor in CVI. But that is not particularly strong evidence. As future research further clarifies the nature and causes of CVI, the mechanisms by which these phlebotonics work can be better substantiated.

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