Pharmacological Agents in the Treatment of Venous Disease: An Update of the Available Evidence

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Abstract: Varicose veins and the complications of venous disease are thought to affect over a quarter of the adult population and the management of these conditions are a major cause of health service expense. Advances in the understanding of venous pathophysiology have highlighted numerous potential targets for pharmacotherapy. This review considers the evidence for pharmacological agents used for the treatment of chronic venous disease.

A literature search using Pubmed, Embase and Cinahl databases was performed. The initial search terms ‘varicose vein’, ‘venous ulcer’ and ‘venous disease’ were used with appropriate search limits to identify prospective studies of pharmacotherapy in venous disease.

A wide range of vеноactive and non-venoactive drugs have been studied in patients with venous disease. The use of micronized purified flavonoid fraction (Daflon) can reduce symptoms of pain, heaviness and oedema in patients with venous reflux and a recent meta-analysis concluded that Daflon improves healing in patients with venous ulceration treated with compression. Pentoxifylline may be a useful adjunct to compression therapy for patients with venous ulceration. Oxerutins and calcium dobesilate may be of benefit in reducing oedema and rutosides may help to relieve the symptoms of varicose veins in pregnancy. The clinical benefits of other medications remain unproven.

Although numerous pharmacological agents have been proposed and studied, Daflon has demonstrated the greatest clinical benefits in patients with venous disease. Further research is needed to define the role of vеноactive drugs in clinical care and improve our understanding of the pathophysiology of venous disease to help identify new therapeutic avenues.

Keywords: Varicose veins, venous disease, pharmacotherapy, vеноactive, phlebotropic, venous hypertension.

INTRODUCTION

The assessment and treatment of patients with varicose veins and the complications of chronic venous ulceration is estimated to consume a 2-3% of the health budget in western countries [1]. The point prevalence of venous disease may be as high as 50% [2, 3]. The severity of venous disease may be classified using the CEAP (clinical, etiologic, anatomic, pathophysiological) system [4] (Table 1) and symptoms including pain, oedema, itching and heaviness may be experienced at all clinical stages of chronic venous disease [5, 6]. The mainstay of therapy remains correction of superficial venous reflux using traditional vein surgery, endothermal ablation or foam sclerotherapy, although compression stockings also have a role. However, stockings may be difficult to put on and uncomfortable to wear and patients are often unwilling to undergo surgical intervention, particularly elderly patients with venous ulceration [7]. Moreover, residual symptoms of chronic venous disease are common despite surgical treatment. For a large number of patients, pharmacological therapy is an appealing treatment option.

Advances in the understanding of venous pathophysiology have highlighted numerous potential pharmacological targets. Systemic drug therapy has been tried for many years in an attempt to reduce symptoms from varicose veins and pharmacologically reduce the chronic skin sequelae of venous hypertension. A large number of naturally occurring and synthetic agents have been shown to have vеноactive properties and in many countries, the use of vеноactive drugs is generally considered as an adjunct to sclerotherapy or sur-

Table 1. CEAP (Clinical, Etiologic, Anatomic, Pathophysiological) Classification of Chronic Venous Disease [4]

<table>
<thead>
<tr>
<th>C Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>C0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C1</td>
<td>Telangectasia or reticular veins</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>C3</td>
<td>Oedema</td>
</tr>
<tr>
<td>C4a</td>
<td>Skin pigmentation and / or eczema</td>
</tr>
<tr>
<td>C4b</td>
<td>Lipodermatosclerosis and/or atrophie blanche</td>
</tr>
<tr>
<td>C5</td>
<td>Healed venous ulceration</td>
</tr>
<tr>
<td>C6</td>
<td>Active venous ulceration</td>
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gery, which are regarded as more definitive treatments. A large number of studies have investigated the efficacy of pharmacological agents for patients with uncomplicated and advanced venous disease.

The aim of this review is to discuss and present the available evidence for pharmacotherapy in the management of patients with symptoms due to chronic venous disease. The prevention and treatment of deep venous thrombosis is considered a separate topic and not reviewed here.

METHODS

A detailed literature search using Pubmed, Embase and Cinahl databases was performed. The initial search terms ‘varicose vein’, ‘venous ulcer’ and ‘venous disease’ were used with appropriate search limits to identify relevant clinical studies of pharmacotherapy in venous disease. Prospective studies, randomised clinical trials and meta analyses were reviewed.

LIMITATIONS OF STUDIES OF VENOACTIVE DRUGS

Although a large number of studies have investigated the efficacy of venoactive drugs in patients with chronic venous disease, a number of general drawbacks can be identified. Symptoms of venous disease including oedema and pain are notoriously difficult to identify or reliably measure, making meaningful assessment of the efficacy of venoactive drugs difficult. This leads to inevitable heterogeneity between studies. Moreover, there is no reliable animal model for venous disease, meaning that the usual extensive investigation that drugs would be subjected to, has not been performed for most venoactive drugs. Many studies testing the efficacy of drug treatment in venous disorders of the leg were carried out in the 1980s or earlier. The applicability of these trials to modern clinical practice should be questioned. These limitations should be considered before drawing conclusions from the available evidence.

OVERVIEW OF MEDICATION USED IN VENOUS DISEASE

Drugs used for venous disease may be classified as either venoactive or non-venoactive (Table 2). For the purposes of this article, venoactive drugs can be defined as a group of naturally occurring or synthetic drugs that act on capillary permeability or venous tone and may therefore have a beneficial effect in patients with chronic venous hypertension. There are 2 principle categories of venoactive drugs: naturally occurring agents and synthetic agents. Their mechanism of action has not been fully elucidated, but they are thought to improve venous tone. Increased venous pressure is associated with microcirculatory changes, namely white cell aggregation and activation with subsequent release of inflammatory mediators, increased capillary permeability, and microthrombus formation [8]. These agents could also act to counter these responses, by decreasing white cell activation and release of inflammatory mediators, decreasing capillary fragility and permeability, and decreasing blood viscosity. It should be noted that although venoactive drugs are widely used in mainland Europe, many are not licensed by the FDA, or available in the United Kingdom.

<table>
<thead>
<tr>
<th>Class / Group</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturally occurring drugs</td>
<td></td>
</tr>
<tr>
<td>Benzopyrones</td>
<td>Coumarine</td>
</tr>
<tr>
<td>Alpha-benzopyrones</td>
<td>Micronised purified flavonoid fraction (MPFF)</td>
</tr>
<tr>
<td>Gamma-benzopyrones</td>
<td>Oxerutin, rutin and rutosides</td>
</tr>
<tr>
<td></td>
<td>Diosmine</td>
</tr>
<tr>
<td>Saponins</td>
<td>Ruscus extract</td>
</tr>
<tr>
<td></td>
<td>Escin (Horse chestnut extract)</td>
</tr>
<tr>
<td>Other extracts</td>
<td></td>
</tr>
<tr>
<td>Proanthocyanidins</td>
<td>Maritime pine tree extract</td>
</tr>
<tr>
<td>Gingko biloba</td>
<td>Gingko biloba</td>
</tr>
<tr>
<td>Synthetic drugs</td>
<td>Calcium dobesilate</td>
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<tr>
<td></td>
<td>Naftazone</td>
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PHARMACOTHERAPY FOR MILD AND MODERATE VENOUS DISEASE (CEAP C1-C4)

Indications for Therapy

For patients with varicose veins without ulceration, medications are usually prescribed for symptom relief. The symptoms most frequently assessed in drug studies are heaviness, fullness, discomfort, cramps, itching, pain, restless legs, sensation of heat and swelling.

Micronized Purified Flavonoid Fraction (MPFF)

MPFF or Daflon® (Servier, France) is a unique composition of diosmine and flavonoid components and is the most studied venoactive agent. The process of micronisation is able to reduce the size of flavonoid particles to around 2 microns, which is thought to improve intestinal absorption [9]. Excretion is predominantly via the kidneys.

Mechanism of Action [10, 11]

Although the precise pharmacokinetics of Daflon remain incompletely understood, it is thought to have numerous modes of action including:
- Inhibition of noradrenaline degradation by catechol-O-methyltransferase and thus indirectly increasing venous tone
- Inhibition of leukocyte adhesion and activation and therefore reducing inflammation
- Inhibition of platelet function
- Increased lymphatic drainage

Evidence for Efficacy

The clinical efficacy of Daflon has been evaluated in a number of clinical trials. Many small studies have demon-
strated an improvement in the symptoms of venous disease in patients treated with Daflon [12-15]. The RELIEF study (Reflux assEssment and quaLity of lIfe improvEment with micronized Flavanoids) was a large European study involving over 5,000 patients treated with Daflon from 23 countries [16, 17]. Significant improvements in patient symptoms, leg oedema, CEAP clinical class and health related quality of life, independent of the presence of venous reflux were reported. Reduction in leg oedema, assessed by calf circumference or volumetric analysis has also been reported by other [14, 18, 19], but not all randomized studies [20].

Recent trials have compared Daflon with oxerutins [21] and the maritime pine tree extract pycnogenol [22]. These studies suggested that Daflon was inferior to both other agents in terms of symptom improvement, but small sample sizes and heterogenous study designs make it difficult to draw firm conclusions from these trials. In recent years, there has been interest in the importance of inflammation as an aetiological factor in the development of venous valve dysfunction [23]. As Daflon has anti-inflammatory actions, this has been proposed as a potential treatment for the prevention of valve incompetence, although reliable evidence of this effect is currently unavailable [24].

**Oxerutin and Other Natural Venoactive Drugs**

Oxerutins and rutosides are made of a mixture of flavonoid derivatives and thought to decrease capillary permeability and reduce free radicals. These drugs may be administered locally or systemically [25] and have been shown to reduce the symptoms of venous disease, particularly swelling and improve haemodynamic venous function in prospective studies [26-28]. Meta analyses of randomised studies have shown that the incidence of symptom relief with placebo is high (in the order of 30%), but additional and significant benefits may be present for patients treated with oxerutin or rutosides [29]. In a randomized placebo-controlled study, 4 different rutoside formulations (500 mg, 300 mg sustained release, 300 mg regular release, and 1000 mg in aqueous solution) were found to be equivalent, but superior to placebo, in reducing leg heaviness after 12-week follow-up of 100 women [30]. A study directly comparing Venoruton and Daflon suggested microangiopathic and clinical advantages for the former [21]. Although not generally endorsed by the manufacturers, rutosides may be beneficial in relieving the symptoms of varicose veins in pregnancy [31]. Oxerutins and rutosides remain commonly prescribed in parts of mainland Europe, but the heterogeneity between studies and the lack of large, recent randomised trials have limited the popularity of these agents in other countries [32].

The alpha-benzopyronone coumarine has been used either alone or in combination with other venoactive drugs for the treatment of lymphoedema and a number of studies have reported favourable results [33, 34]. However, the risk of hepatotoxicity has dramatically limited the use of coumarine. With such a huge range of agents potentially available, many studies have investigated the effectiveness of other venoactive drugs (or their combinations). Studies of Escin [35] (reduce capillary filtration), Ruscus extracts [36] (reduce capillary permeability), Ginkgo biloba [37] and proanthocyanidines, such as the maritime pine tree bark extract [38] have been performed, but only limited clinical benefits were observed and sample sizes were generally small. Of note, a recent Cochrane review identified 44 randomised trials of venoactive drugs for the treatment of chronic venous disease, but concluded that the available evidence was insufficient to support the routine use of these agents [39].

**Synthetic Venoactive Agents**

Calcium dobesilate is a synthetic agent thought to increase lymphatic drainage and may increase venous tone and has been evaluated in a number of randomized studies. A meta analysis published in 2004 and other randomized studies demonstrated significant improvements in oedema, symptoms and lymphatic drainage in patients treated with calcium dobesilate compared with placebo [40-42]. However, the largest randomized study of calcium dobesilate was recently published [43] and 509 patients were randomized to either calcium dobesilate or placebo. There were no differences between the study groups in terms of disease specific quality of life, swelling or symptoms at 3 months [43]. This recent evidence has raised doubts of the true efficacy of calcium dobesilate and further studies are needed to confirm the clinical benefits demonstrated by early trials. A placebo-controlled trial of naftazone in primary uncomplicated varicose veins claimed a statistically and clinically significant improvement in disability scores as subjectively assessed on a visual analogue scale [44], although other clinical studies are scarce.

**PHARMACOTHERAPY FOR CHRONIC VENOUS ULCERATION (CEAP C6)**

The most widely studied venoactive drug for the treatment of chronic venous ulceration is Daflon and a meta-analysis published in 2005 pooled the results of five randomised clinical trials including 723 patients [45]. The authors concluded that adjuvant treatment with Daflon conferred an additional 32% chance of healing in patients with chronic venous ulcers and the median times to healing were 21 weeks in the control group compared to 16 weeks for patients treated with Daflon [45]. Clinical trials of oxerutins or horse chestnut seed extract have failed to demonstrate a clinical benefit in patients with ulceration [46, 47].

**RISKS OF VENOACTIVE DRUGS**

In general, the safety and side-effect profile of venoactive drugs is good, although hepatotoxicity has been associated with coumarine [34]. Gastrointestinal adverse effects are most common and may include nausea, vomiting, colicky abdominal pain, insomnia, drowsiness and headaches [48]. Side effects may be experienced by up to 5% of patients [49]. Most manufacturers recommend avoiding venoactive drugs during pregnancy or breastfeeding, although some agents have been used in the second and third trimesters [50]. The use of multiple venoactive drugs at the same time is generally discouraged [49].

**THE USE OF NON VENOACTIVE DRUGS IN THE TREATMENT OF VENOUS DISEASE**

The non-venoactive drug category has only been used predominantly in the management of patients with venous
ulcers, and includes pentoxifylline (fibrinolysis and reduction of white cell activation), stanozolol (lysis of ‘fibrin-cuff’), ergotamine (vein wall contraction), prostaglandins (small vessel dilatation, platelet inhibition) and aspirin (platelet inhibition). Pentoxifylline is well tolerated and for patients with venous ulcers, a number of studies have suggested that pentoxifylline may have a role in accelerating ulcer healing [51, 52], although others have failed to demonstrate a significant effect [53]. A recent Cochrane systematic review concluded that pentoxifylline may be an effective adjunct to compression for patients with chronic venous ulcers [54], although the clinical benefits of treating patients with venous ulceration remains debatable. Although a small randomized study demonstrated a clinical benefit for 300 mg of aspirin compared with placebo in patients treated with compression for venous ulcers [55], these findings have not been reproduced in other studies. Non-randomised studies have been published, but there is no level 1 evidence supporting the use of stanozolol, ergotamine or prostaglandins for the treatment of venous disease.

DISCUSSION

The effective amelioration of the symptoms of venous disease using pharmacotherapy and therefore avoiding the adverse events of surgery is an attractive and desirable goal. Numerous natural and synthetic venoactive drugs have been proposed and tried to provide effective treatment for the symptoms of chronic venous insufficiency. Perhaps the most popular drug and that with the greatest body of evidence is Daflon (micronized purified flavonoid fraction). Randomised studies have demonstrated significant improvements in objective symptom scores and disease specific quality of life [15, 18]. Moreover, there is evidence that venous ulcer healing with compression bandaging may be augmented with Daflon [45]. Significant improvements in symptoms attributable to chronic venous disease have also been reported in patients treated with calcium dobesilate, oxerutins and rutosides [28, 40].

Interestingly, many clinicians involves in the treatment of patients with chronic venous disorders have not embraced the use of venoactive drugs. This may be partly explained by the fact that studies have been generally small and heterogeneous and outcomes are difficult to measure, which has limited the acceptance and availability of venoactive drugs in many countries. Furthermore, a huge and confusing variety of venoactive drugs (and combinations) have been evaluated, limiting the application of the available evidence.

The lack of universally accepted and effective pharmacotherapy for venous disease highlights the multifactorial nature of the symptoms suffered by these patients. Factors such as obesity, calf muscle pump function, comorbidity (particularly cardiac disease) and other medication may all contribute to the symptoms thought to originate from venous incompetence. Clearly a pharmacological panacea for these patients is unrealistic and a holistic, multidisciplinary approach must underpin their clinical management. For many patients, it is likely that surgical ablation of refluxing superficial veins using traditional surgery, endovenous laser therapy, radiofrequency ablation or foam sclerotherapy will be the most effective long term strategy for the treatment of venous symptoms.

A growing body of evidence has implicated inflammation and hypoxia as key processes in the development of venous valvar incompetence and chronic venous hypertension [24]. The use of venoactive agents, particularly Daflon to prevent this process is an exciting potential therapeutic avenue. Rat models have demonstrated that Daflon is extremely effective at protecting against the inflammatory changes induced by venous hypertension [56]. The results of large longitudinal studies will help identify if this protective effect is as potent in humans.

In conclusion, many studies have evaluated the clinical benefits of venoactive agents in patients with chronic venous disease. Daflon or Micronized Purified Flavonoid Fraction has been shown to reduce the symptoms of venous disease, particularly oedema and may improve venous ulcer healing as an adjunct to compression therapy. Calcium dobesilate, oxerutin and rutosides may also have similar clinical benefits. Further large randomised studies are needed with objective, universally accepted end-points to define the precise roles of the venoactive drugs. Only then can we reach an international consensus on the precise role of Daflon and other drugs, with surgery and compression therapy in the treatment of patients with chronic venous disease.

REFERENCES

Pharmacological Agents in the Treatment of Venous Disease


