Review Article

CHRONIC VENOUS DISEASE AND VENOUS ULCER: PHARMACOLOGICAL APPROACH

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ABSTRACT

Background: *Pharmacological treatment of venous diseases is common, but there is considerable international variation in the use of drugs. The purpose of this study is to review the clinical evidence.*

Methods: *A systematic literature review (1966-2000) was carried out.*

Results: *144 studies were identified and considered for review. A wide range of drug types is used of which the 'venotonic' drugs are the most numerous. Some members of this group reduce oedema and symptoms compared to placebo. Diosmin and hesperidin may accelerate venous leg ulcer healing.*

The anabolic steroid stanozolol reduces the area of lipodermatosclerosis when used in combination with stockings but has the disadvantage of androgenic side effects. In the management of venous ulceration, Ifetroban and antibiotics are ineffective and aspirin has not been properly evaluated outside a very limited pilot study. Oxpentifylline has been shown to have a wound healing effect in some studies.

Conclusion: *Drugs are widely used in the management of venous diseases, but none abolishes varicose veins or venous ulcers. Some venotonic drugs reduce the symptoms of venous disease including oedema. A few studies show modest efficacy in leg ulcer healing. There is considerable scope for the development of more effective drugs in the treatment of chronic venous disease.*

Keywords: *Chronic Venous insufficiency, venous ulcer, drug treatment.*

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INTRODUCTION

Venous valvular incompetence of lower limb veins leads to chronic venous disease (CVD). This may result in symptoms varying from uncomplicated varicose veins to oedema, liposclerotic skin changes and ulceration. A recent epidemiological study found that varicose veins arise in 40% of men and 32% of women, with skin changes attributable to venous disease in 9% of men and 7% of women, a risk that increases with age[1]. In the UK, 150 – 200,000 patients receive treatment at any one time for leg ulceration. An estimated population 1 - 2 millions is at risk of ulceration[2-4].

It is widely accepted that incompetence in deep or superficial veins results in the clinical symptoms of skin changes and leg ulceration[5]. Surgical treatments are directed towards removing incompetent superficial veins, ligating incompetent perforating veins and sometimes restoring the competence of deep veins.

Compression bandaging and stockings remain effective treatments in the healing of ulceration and management of trophic skin changes[6]. The combination of surgical and compression treatments remains the mainstay of management for patients with venous disease. However, these have their limitations. There are a substantial proportion of patients in whom there is a deep vein problem. Few of these patients are suitable for deep vein reconstruction. Compression treatment heals most venous ulcers, but 20 – 25% of these patients suffer recurrence of their ulceration[7]. Trophic skin changes resulting from venous disease can be treated using the same principles. Many patients find wearing compression stockings in the long term a considerable imposition on their lives, especially in warm weather.

In addition, it is the microcirculatory consequences in the skin of venous hypertension that give rise to the trophic skin changes and ultimately to ulceration[8-10]. Many abnormalities of the microcirculation have been identified. These include leukocyte sequestration during venous hypertension, platelet sequestration, endothelial activation and reduced oxygen tension in the skin. Pharmacotherapy may be a useful adjunct in the treatment of venous leg ulcers by addressing some of these processes, which affect the microcirculation. There is, therefore, considerable scope for drug treatment in patients with venous diseases, assuming that suitable drugs can be developed.

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METHODOLOGY

In order to achieve a thorough evaluation of the publications on the drug treatment of chronic venous disorders of the leg, articles were identified using three methods. First computerized literature searches were performed using the Medline database for the years 1966-2000. Keywords searched were drugs, venous diseases of lower limbs, venous ulcer, leg ulcer, pharmacological treatment, drug therapy, chronic venous insufficiency treatment and clinical trials. Secondly, a manual search, focusing on randomized clinical trials of the pharmaceutical treatments, was conducted in selected scientific journals that were for the most part not listed in Medline. This included phlebology. Finally, manufacturers' brochures of the drugs were consulted and further information acquired from them, where it was felt necessary. Cochrane library database for randomised clinical trials were also searched. Most of the articles are written in English; occasionally translated versions of French and German papers were considered. Whilst the authors would have preferred to include only randomised controlled trials in this review, many drugs currently used in the treatment of venous diseases have never been tested in this way! Papers describing studies of other designs have been included to provide as much information as possible about each drug group mentioned below.

RESULTS

Many of the studies were found to be old (published more than 10 years ago). In many cases these contained the only information about some drugs and have been included. The number of papers identified, which fulfil search criteria is 144.

At present, drugs act as an adjuvant for compression therapy for venous ulcers and for symptoms relief in CVI with the objective of increasing venous tone[11, 12] stimulating lymph drainage[13-16] and protecting the microcirculation from products released by the activated leucocytes[17-19].

Drugs tested in patients with venous disorders may be classified into three broad categories:

1. Venoactive drugs whose indications are specific to venous disorders;
2. Non-venoactive drugs which have been tested for specific use in patients with venous disorders; and
3. Topical drugs to treat venous ulceration.

Venotonic (Venoactive or phlebotropic) drugs

Drugs, which address the symptoms of venous disease but do not influence valvular competence or other aspects of the macro-physiological problem, are described as 'venoactive drugs'. Most venoactive drugs are derived from plants. They consist of pure substances, plant extracts and synthetic molecules copying the plant original, combinations of several active substances or even a plant extract where the composition remains unknown. These drugs are widely used for the medical treatment of venous disorders and costs for drug treatment for symptoms in 1983 extrapolated to 1990 in France was 3.35 billion FF[20]. Their main indications are symptoms (aching, discomfort, 'restless legs') and oedema, which reflects the clinical presentation of patients in most cases.

Venoactive drugs may act at several levels of the pathophysiological pathway leading to clinical manifestations of CVD. They may improve venous tone, which is reflected by a decrease in the distensibility of the venous wall, expressed as compliance[11, 21, 22]. There are evidences that they can act on the following microcirculatory parameters to:

1. Decrease White Blood Cells (WBC) sticking and activation[23, 24]
2. Decrease production of inflammatory mediators[25]
3. Decrease capillary permeability[26]
4. Decrease capillary fragility[27]
5. Decrease blood viscosity[28]
6. Improve transcutaneous partial pressure of oxygen ($TcPO_2$)[29]

An additional effect on lymphatic pumping has also been shown[13-16].

Classification of the venoactive drugs

Table 1 summarises a simple classification of the drugs used to treat venous disease[30, 31].

These drugs are too often considered to be drugs of secondary value and of doubtful efficacy in the treatment of venous diseases. However, a better understanding of the pathophysiology of venous insufficiency and the development of objective and reproducible investigation techniques, as well as the rigorous methodology of recent clinical trials, have demonstrated the efficacy and clinical value of these drugs[32, 33]. However, it is fair to say that used alone, none cures varicose veins or venous ulceration; it is the symptoms of venous disease, which are addressed.

Flavonoids: Daflon 1

Daflon is a micronized purified flavonoid fraction (MPFF) containing a mixture of two flavonoids: diosmin (90%) and hesperidin (10%).

Table 1. Classification of venoactive drugs

Type of drug	Group	Sub-group	Names of compounds
Natural products:	Benzopyrones	α- Benzopyrones	Coumarin (1,2-benzopyrone; 5,6- α-benzopyrone), melitot coumarinic derivatives Esculetin (6,7-dihydrooxycoumarin) Umbelliferone (7-hydroxycoumarin) Dicoumarols (dimers of 4-hydroxycoumarins): oral anticoagulants
		γ- benzopyrones (flavonoids)	Flavone and flavonols: - Diosmine , kaempferol, diosmetin, quercetin, - rutine and derivatives, troxerutine, O-(β-hydroxyethyl) rutosides (HR or oxerutins)
			Flavanes and flavanones: - Hesperetin, hesperidene, catechin, methylchalcone, flavonoic acid
	Saponosides:		- Aescine, horse-chestnut extracts (protoescigenin, barringtogenol, α-and β -escin, cryptoescin) - Extracts of Ruscus (ruscosides), Centella asiatica
	Other plant extracts	Anthocyanosides	Blueberry extract
		Pycnogenols	Leucocianidol, Procyanidolic oligomeres: grape seed extracts
		Ginkgo biloba	
		Ergot derivatives	Dihydroergotamine, Dihydroergocristine, Dihydroergocryptine
Synthetic products			- Calcium dobesilate - Benzarone - Naftazone - Tribenoside - Chromocrabe - Diethylamine - Adenosine phosphate - Heptaminol

Symptom relief

Efficacy of this drug in symptomatic treatment of CVD is well known and has been documented in double blind trials in human subjects[27,34,35]. Daflon produced a significant decrease in venous capacitance, venous distensibility, and venous emptying time ($p < 0.001$), in addition to the improvement in clinical symptoms and a decrease in the supramalleolar circumference[22]. The efficacy of micronized diosmin has been demonstrated in various double blind studies[21, 34, 36, 37]. After two months, treatment with micronized diosmin resulted in a statistically significant improvement of symptoms and signs of functional and organic venous insufficiency, including a reduction of supramalleolar circumference. It was also claimed that the drug led to disappearance or improvement in skin changes in 88% of micronized diosmin patients compared to 21% treated with placebo. In a randomized, double blind, placebo-controlled trial of 105 patients with active ulcers, Daflon was used as an adjunct to compression therapy and standard wound care. Patients with an ulcer size less than 10 cm receiving Daflon ($n = 14$ out of 44) fared better than those receiving placebo ($n = 6$ out of 47); 32% vs 13%, ($p = 0.028$) with a significantly shorter time duration of healing ($p = 0.037$) in the active treatment group[38]. Among the 14 patients with ulcer size > 10 cm (Diosmin = 9, Placebo = 5) no ulcer healed. This study showed that a two-month course of Daflon 500 mg at a daily dose of two tablets, in addition to conventional treatment, is of benefit in patients with venous ulcer < or = 10 cm by accelerating complete healing. There is no data to suggest that this drug influences the size or extent of varicose veins.

Mechanism of action

The mode of efficacy of this drug is incompletely understood. Flavonoids have several anti-inflammatory actions.

In a study[39] of the effects of Daflon on the microvasculature in the cheek pouch preparation of diabetic hamster, the flavonoid significantly inhibited the macromolecular permeability. Flavonoid-treated hamsters also tended to have a lower number of leucocytes adhering to the venular endothelium in ischaemia-reperfusion injury.

In another double blind, placebo controlled randomised trial, flavonoid fraction was found to increase the 'capillary resistance' as evaluated by the negative suction cup method. This study was carried out in patients with capillary fragility who were treated for six weeks with significant improvement of symptoms of capillary fragility[27]. Daflon 500mg (2 tablets daily for six weeks) also reduces the capillary permeability as revealed by a decrease in the retention of initially high, labelled albumin (Tc^{99m} albumin test) in patients suffering from idiopathic cyclical oedema as demonstrated in a double blind placebo controlled study[26].

Inflammatory Mediators in animal studies

In a study performed in rats[40] Daflon 100 mg per day was administered by intubation and an inflammatory granuloma was formed by implantation of polyurethane sponges in treated rats and control animals. Daflon 500 mg reduced oedema formation, inhibited the synthesis for PGE_2 (78.5%), PGF_2 alpha (45.2%) and TXB_2 (59.5%) and improved the multiple histological aspects of acute and chronic inflammatory reaction[25].

Haemorrheological

An open pilot study using 6 weeks treatment with Daflon was performed to verify the variations in capillary packed cell volume in comparison with the velocity in 24 patients with third stage CVD. Ankle skin microcirculation was evaluated by dynamic capillaroscopy, relative capillary packed cell volume was calculated by a densitometric method and the red blood cell velocity was calculated using the simplified cross-correlation method. Daflon 500 mg significantly increased the velocity of the

red blood cells after 4 weeks treatment and after an initial increase; Daflon ultimately decreased the relative intracapillary haematocrit after 6 weeks treatment, suggesting an increase in the deformability of red blood cells[28].

Free Radicals and Oxidation in animal studies

Flavonoids have been used in the treatment of vascular endothelial damage. The values of their scavenging rate constants are only 30 times less active than that very potent endogenous NO scavenger, haemoglobin. It is speculated that NO scavenging plays a role in the therapeutic effect of the flavonoids[41]. In an animal model, intravenous injection of Daflon (25 and 50 mg/kg) reduced the hyperglycemia induced by injection of alloxan in the rat[42]. This effect of Daflon was linked to its ability to scavenge active oxygen radicals, demonstrated in vitro using human neutrophils or mouse peritoneal macrophages stimulated by zymosan[25]. Flavonoids and many other phenolic compounds show a wide range of antioxidant activities in vitro. It has been shown that flavonoids can interact with hydroxyl free radicals[43, 44].

Xanthine Oxidase Inhibition in animal studies

Flavonoids have been demonstrated to inhibit beef heart mitochondrial succinoxidase and NADH-oxidase activities. Flavonoids possessing a catechol configuration exhibited a slow rate of auto-oxidation in buffer that was stimulated by the addition of CN^-. The addition of superoxide dismutase (SOD) and catalase in the auto-oxidation experiments each decreased the rate of oxygen consumption, indicating that O_2^- and H_2O_2 are generated during auto-oxidation. In the CN^- stimulated oxidation experiments, the addition of SOD also slowed the rate of oxygen consumption. These findings demonstrate that the CN^-/flavonoid interaction generated O_2^- non-enzymatically, which could have biological implications[45].

Effects on $TcPO_2$ and laser Doppler parameters

The effect of Daflon on the microcirculation in man has been investigated in a study in which laser Doppler fluxmetry, transcutaneous oxygen and carbon dioxide levels were assessed in the skin[29]. Patients with mild venous disease (no skin changes) were randomised to receive 500mg, 1g or 2g of Daflon per day. Small increases in $tcPO_2$ and decreases of $tcPCO_2$ were observed in all groups after three months treatment, with no difference seen between the different dosage regimes. No changes in laser Doppler flux were found. Since patients without skin changes show only minor disturbances in $tcPO_2$ and $tcPCO_2$ levels the scope for improvement in these measures of mild venous disease is limited. It is only in liposclerotic skin that these parameters show large changes and where improvement would be significantly beneficial following any treatment.

Evidence of leucocyte activation in animal studies

Studies using fluorescence intravital microscopy in the post capillary venule of the hamster skin fold suggested that pre-treatment with Daflon prior to the induction of ischaemia significantly lower the number of leucocytes adherent to the endothelium. The group of animals pretreated with Daflon exhibited less neutrophil adhesion in the post-capillary venules at reperfusion, compared to the control group[24]. This observation has been speculated to be linked to the protective effect of flavonoids in the treatment of oedema, as decreased activation is also associated with a decreased platelet and complement system activation, leading to a lowered release of histamine and decreased leucocyte-dependent endothelial damage[46]. In another model of the microcirculation, small bowel and cremaster of rats, Korthuis showed that Daflon inhibits leukocyte adhesion and migration induced by ischaemia/reperfusion[47, 23]. Basal expression of ICAM-1 was not modified, but Daflon markedly reduced the increased expression of ICAM-1 after 4 hours reperfusion. In contrast, post ischaemic P-Selectin expression was not modified by Daflon treatment[48]. In a rat model of venular occlusion, treatment with Daflon® significantly decreased the number of rolling, adherent and migrating leucocytes in the rat mesentery[49]. Daflon reduced neutrophil expression of CD62L, even though CD18 was not affected[50]. Bouskela has also confirmed this in the hamster cheek pouch model of the microcirculation[23]. These data from animal studies suggest that Daflon acts as an anti-inflammatory drug by reducing leukocyte adhesion.

Effect on leucocyte adhesion and endothelial activation in human studies

A recent pilot study has been conducted at the Middlesex Hospital vascular laboratory using Daflon®. 20 patients with chronic venous disease (CEAP clinical stage 2-4) were treated for 60 days with Daflon® twice daily taken orally. The expression of the leukocyte adhesion molecule CD62L was substantially decreased on monocytes and neutrophils by Daflon treatment, however, CD11b expression was not modified. This finding suggests that leucocyte L-selectin interaction with endothelial selectins

responsible for the initial stages of adhesion may be modulated by Daflon, reducing the likelihood of leucocyte adhesion and presumably acting as an anti-inflammatory treatment.

Significant down regulation of plasma levels of VCAM-1 and ICAM-1 activity following therapy was also noticed indicating that endothelial damage in venous disease is mitigated by Daflon treatment. In this study the plasma VEGF levels decreased in patients with stage C4 chronic venous disease after treatment with Daflon (98-57 pg/ml), but not in patients with stages 2 and 3 [19]. These findings may suggest possible mechanisms by which Daflon exerts an effect and improves venous ulcer healing[38]. In any case, it is further evidence of mitigation of the inflammatory responses in CVD by MPFF. Further investigation is needed to confirm these findings in a randomised double blind placebo controlled study in different groups of patients.

Hydroxyethylrutosides (Oxerutins, Paroven®[3])

Hydroxyethylrutosides is a standardised mixture of semi-synthetic flavonoids, mainly mono-, di-, tri-, and tetra hydroxyethylrutosides, which acts primarily on the microvascular endothelium to reduce hyperpermeability and oedema. This drug and troxerutine have also been used with variable effects on CVD symptoms.

Adverse effects of flavonoids

Reported adverse events with drug therapies are nausea, headache, gastric pain/cramps and insomnia. There do not appear to be significant differences between agents in the frequency of side effects, although certain adverse events are more common with certain drugs.

Calcium dobesilate, a synthetic venotonic, has been tried in various clinical trial with certain efficacy and Horse chestnut extract, Coumarine rutine, Dihydroergotamine, Red vine leaf extract (RVLE) have also been used with limited success in some symptoms relief.
These have been summarised in the table 2.

Non-Venoactive drugs

A variety of other systemic drugs have been used in patients with venous disorders especially for ulcers.

Diuretics for oedema, Antimicrobials, Zinc, Fibrinolytic agent stanozolol, Defibrotide, Haemodialysate, Naftidrofuryl (Praxilene® 4), Flunarizine, Aspirin, Ifetroban, Protease inhibitor such as Plasminogen and Various medicated dressings have also been evaluated in ulcer healing in various trials with very limited efficacy.

Antimicrobials

Frequently antimicrobials are administered to patients with venous ulcers because of perception that bacterial contamination interferes with the healing process. However,

Table 2. Drugs used for relief of venous symptoms

Symptoms	Drug with efficacy shown in clinical trial
Heaviness	Diosmin[21], Coumarine rutine[71], Dihydroergocristine[76], Rutosides[77], Calcium dobisilate[69]
Discomfort	Calcium dobisilate[69]
Cramps	Calcium dobisilate[69], Rutosides[78], Dihydroergocristine[79], Coumarine rutine[71]
Pain and aching	Micronized Diosmin[21], Calcium dobisilate[69], Dihydroergocristine[79], Coumarine rutine[71]
Sensation (subjective symptoms) of swelling	Rutosides[78]
Tightness and paraesthesia	Dihydroergocristine[76]
Restless leg syndrome	Calcium dobisilate[69]
Paraesthesia	Calcium dobisilate[69], Coumarine rutine[71]
Fatigue, tiredness and tenderness	Rutosides[78]
Sensation of warmth	Dihydroergocristine[79]
Global symptoms	Ruscus aculteatus[80] for 8 weeks, calcium dobesilate for 4 weeks[69], Daflon 500mg [81] bd for 4 weeks, hydroxyrutosides in skin changes group (Widmer class 2)[61]

there is no relationship between bacterial findings from microbiological studies and the clinical impression of whether or not the ulcer is infected. Generally even clinically clean ulcers contain a large number of staphylococcus aureus, gram-negative bacteria or mixed cultures with haemolytic streptococci of various groups or anaerobic bacteria. Healing is however, independent of the presence of bacteria in the ulcer[51]. There is no evidence to show that antibiotics speed the healing of venous ulcers where there is no clinical evidence of infection e.g. cellulitis.

Drugs that modify leucocyte metabolism

Disappointment with existing pharmacological treatments has led to the search for alternative lines of drug treatment on venous skin damage. The discovery of the involvement of leucocytes in the development of venous ulceration has opened new avenues of investigation in this area[37]. Two drugs, which modify white cell activation prostaglandin E_1 (PGE_1) and the prostacyclin analogue Iloprost 3 did not show any convincing benefits in ulcer healing.

Pentoxifylline (Trental®[6])

Pentoxifylline has been used for the treatment of claudication for a number of years, with moderate success[52]. It has been shown that it actually has a potent effect on inhibition of cytokine-mediated neutrophil activation, which appears to be independent of other known activators of neutrophils such as TNFa [53]. They also showed it to reduce white cell adhesion to endothelium and to reduce the release of superoxide free radicals produced

in the so-called respiratory burst characteristic of neutrophil degranulation.

In a rigorous multi-centre placebo-controlled double blind prospective study[54] of 80 patients with venous ulcers, pentoxifylline has been shown to result in statistically significant better healing rates of ulcers than placebo. A randomised, double blind placebo controlled trial, parallel group study of factorial design, permitting the simultaneous evaluation of alternative pharmaceutical, bandaging, and dressings materials was performed by the same authors in 200 patients with confirmed venous ulcers using Pentoxifylline 400 mg three times daily or placebo. It showed complete healing occurred in 65 of the 101 (64%) patients receiving pentoxifylline and 52 of the 99 (53%) patients receiving placebo. The difference in the healing rates between patients taking pentoxifylline and those taking placebo did not reach statistical significance[55]. The difference that they found (64% healing with pentoxifylline v 53% healing with placebo) would probably be clinically useful in view of the high material and labour cost of continuing treatment with pressure bandaging and the unpleasantness of leg ulcers. The study described only had a 30% power to detect this magnitude of difference. To have an 80% power to detect this difference would require a study with 332 in each group.

Dressings and topical drugs

Dressings should provide a stable, non-adherent contact layer, which promotes hydration of tissue as well as gas exchange. The dressings should also have the capacity to absorb excess fluid. Any system for preventing or treating local infection should not employ chemicals, which may be toxic or inhibitory to regenerating epithelial cells. Since the major objectives in the local treatment of venous ulcer are to prevent desiccation and infection so that epithelial cells can regenerate, dressings should not become incorporated into the wound (unless they are biodegradable) and should not tear fragile epithelium when removed.

Dressings are used frequently for the treatment of leg ulcers, but there have been few well controlled clinical trials assessing their efficacy. This review does not aim to evaluate all marketed dressings, but focuses instead on well designed studies of the therapeutic efficacy of dressings. Several types of dressing have been tested.

Among these, cadexomer iodine (Iodosorb[7]) has shown better results when compared to standard dressings[56, 57]. Its effects on ulcer healing and factors related to ulcer healing such as the presence of pus and debris, exudate, erythema, and oedema has been shown. Inclusion criteria for entry in these trials were unhealed ulcer for at least 3 months or failure of current treatments. The results of a hydrocolloid dressing[58] and of dextranomer beads[59] have not demonstrated the same efficacy.

Topical application of synthetic human growth hormone[60] demonstrated significant effects, with 61% of patients experiencing healing of more than 50% of ulcer size, compared to 18% of patients receiving placebo. These promising results require confirmation in larger study, as that study was very small.

DISCUSSION

Symptoms of venous disease

Phlebotropic drugs act mainly on oedema and the subjective symptoms of CVI such as heavy legs, 'weightiness', discomfort, pruritis, pain along the course of varicose veins or non specific symptoms including paraesthesiae, night cramps, restless leg. There is no suggestion that they result in the regression of varicose veins.

They are appropriate for the symptoms of venous insufficiency or as adjuvant treatment in a post-thrombotic syndrome. Drug treatment cannot replace elastic support, sclerotherapy or surgery, the only methods capable of eradicating varicose veins attributable to superficial venous incompetence.

Not all drugs have the same effect on all symptoms. The choice of medication for symptomatic treatment should be based on the specific symptoms presented by the patient. The response to a particular drug should be closely monitored.

Table 2 summarises the drugs proved to have efficacy in treating venous symptoms.

These drugs have efficacy for oedema secondary to venous disease and could be used for this purpose as a temporary or permanent solution.

Diosmin[21]
Rutosides[61-68]
Calcium dobesilate[69, 70]
Coumarine rutine[71]

Drug treatment for skin changes

There is very little scientific evidence regarding the efficacy of treatments for skin changes. In most studies, the presence of skin changes was not assessed or is not used as an in measure of the outcome of treatment. Furthermore, skin changes are rarely used as a primary endpoint. Stanozolol is the only drug, which has been shown to reduce the area of lipodermatosclerosis when used in combination with stockings. However, this has the problem of androgenic side effects since it is an anabolic steroid. In any case, it has now been withdrawn. The

results of treatment are generally poorly described, and little quantitative information is provided about the extent of improvement achieved. However, following drugs may be used for symptomatic skin changes group where surgery is not contemplated.

Daflon® [21]

Defibrotide[72] (as adjuvants to compression)

Ulcer healing drugs

No drug has been shown to be effective when used alone. Neither has any drug been found which can achieve healing rates equal to those of high compression bandaging. However, a small number of drugs are available which have a measurable benefit when used to treat patients with venous leg ulcers:

Daflon[38, 73]

Oxpentifylline[74], (but subsequent studies did not confirm these results[75])

Local therapy

Cadexomer iodine dressings[56, 57]

Synthetic human growth factor[60]

No drug has been shown to prevent the recurrence of ulceration following healing. No drug is claimed to have any influence in reducing the size of varicose veins or telangiectases.

The mechanisms of action of many of these drugs remain unknown at the molecular level. Recent information has been published concerning the mechanisms of action of a member of the flavonoid group, Daflon (diosmin and hesperidin). These suggest that a number of anti-inflammatory effects are achieved by these drugs. Leucocyte adhesion to endothelium is inhibited in animal models and in patients reduced endothelial adhesion molecule shedding has been found. The mechanism of the anti-oedema effect of these drugs has still not been clarified.

CONCLUSION

The main methods of treating chronic venous insufficiency continue to be physical: elevation of the limb, compression hosiery, cleaning, dressing and skin grafting of ulcers and surgical correction of superficial or perforating vein incompetence where appropriate. No drug has been shown to be more effective than these treatments in healing venous ulcers or preventing their recurrence.

A role for drug treatment has been demonstrated in relieving the symptoms of venous disease and reducing venous oedema. The drugs, which have most effects, are the rutins and flavonoids. Daflon has demonstrated an ability to prevent damage to the microcirculation in animal models of ischaemia-reperfusion injury. This appears to be based on prevention of leucocyte adhesion. Similar biochemical effects have been found in clinical studies and there is some data to show increased ulcer healing following treatment with Daflon.

A considerable amount of work has been done to elucidate the pathological mechanisms at work in this disease, but the exact sequence of events, which leads to leg ulceration, has yet to be established. More complete understanding of these combined with knowledge of how existing drugs showing some efficacy achieve their effect will help in selecting the correct profile of activity for drugs to be used in the management of venous diseases. Advances in drug treatment appear to offer the next avenue of advance in the treatment of venous disease. We believe that adjuvant pharmacological treatment will eventually be common place in the management of chronic venous insufficiency and venous ulceration.

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