Pharmacology of vasoactive drugs

Farmacologia de drogas vasoativas

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ABSTRACT

Peripheral vascular diseases (PVDS) are characterized as a circulation problem in the veins, arteries, and lymphatic system. The main therapy consists of changes in lifestyle such as diet and physical activity. The pharmacological therapy includes the use of vasoactive drugs, which are used in arteriopathies and venolymphatic disorders. The goal of this study was to research the scientific literature on the use and pharmacology of vasoactive drugs, emphasizing the efficacy of their local actions and administration.

Keywords: Peripheral Vascular Diseases, Pharmacology, Review Literature as Topic

RESUMO

As doenças vasculares periféricas (DVPS) caracterizam-se como um problema de circulação nas veias, artérias e sistema linfático. O tratamento primordial para as DVPS é a mudança de hábitos de vida, alimentação e prática de atividade física. A terapia farmacológica inclui a utilização de drogas vasoativas, as quais são utilizadas nas arteriopatias e nas doenças veno-linfáticas. O objetivo deste estudo foi pesquisar em literatura científica sobre a utilização e farmacologia das drogas vasoativas, enfatizando a eficácia da administração e ação local dessas drogas.

Palavras-chave: *Doenças Vasculares Periféricas, Farmacologia, Literatura de Revisão como Assunto*

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INTRODUCTION

Peripheral vascular diseases (PVDs) encompass a group of chronic degenerative diseases and syndromes that affect the arterial, venous, and lymphatic systems and that are characterized by a narrowing, and/or a blockage of the vessels that conduct blood or lymph to the arms and legs, thereby jeopardizing the normal flow. This hampers the exchange of material between the blood and the tissues, the supply of nutrients, the removal of metabolic waste, and the defense and repair of the tissues. A hypoxic decline of the tissues is related to a series of painful affections of the musculoskeletal machinery such as chronic tendinopathies (tendonitis), degenerative arthropathies (arthrosis), and compressive syndromes of the peripheral nerves (CSPN). These characteristically present pain that is hard to control with non-steroidal antiinflammatories (NSAIDS) or systemic analgesics, impacting significantly on the sufferer's health and quality of life. The arterial PVDs, mainly characterized by atherosclerosis, present intermittent claudication, pain while resting, and trophic lesions as their main symptoms. The symptoms of venous PVDs include the appearance of varicose veins, pains, edemas, and venous thromboses.[1]

When the passage for oxygen and blood is compromised in a certain region drugs can be used that have vasodilating effects or prevent platelet aggregation. The vasodilators can act in diverse ways. Calcium channel blockers show some actions such as increasing local blood flow and reducing arterial pressure or central venous pressure. Activators of the potassium channel bring a hyper-polarization and relaxation of the cell membrane of the smooth vascular musculature. There are other vasodilating drugs that increase the cellular concentration of cyclic adenosine monophosphate (cAMP), of cyclic guanosine monophosphate (cGMP), and even by inhibiting the enzyme phosphodiesterase. The direct-acting vasodilators work by inhibiting sympathetic vasoconstriction and the renin-angiotensin system.[2] The vasoactive drugs, therefore, are useful in the treatment of ischemic and painful conditions of the musculoskeletal machinery.

The pharmacology of drugs used in venous and lymphatic disorders consists mainly of increasing the tone of the venous wall, modifying the microcirculation parameters, reducing capillary hyper-permeability and blood viscosity, and improving the partial pressure of oxygen, leading to a more efficient veno-lymphatic return, and minimizing sanguinary stasis and edema in the extremities. These are considered the main factors responsible for the constant problems of turgidity in soft tissues in areas traumatized by accidents or surgeries, causing a reduction in the range of movement of the articulations involved.[3]

METHOD

The strategy of a bibliographical research was carried out using the following databases: Pubmed, Medline, Bireme base (Virtual Health Library), Scorpus, Science Finder and the Cochrane Library, in addition to didactic books. All available years were researched using the following key-words and relevant phrases: Peripheral vascular diseases, venous insufficiency, vasoactive drugs, mechanism of action of vasoactives, Pentoxifylline, topical buflomedil, local administration of vasoactives, intradermal heparin, local hydergine, codergocrine mesylate, topical verapamil, coumarin, rutin, topical melilotus, topical escin, calcium dobesilate and tribenoside.

Drugs used in arterial diseases

A favorable systemic effect on the circulation was expected from the first drugs with vasodilating action, however undesirable effects were observed. Aside from the central hypotension causing discomfort, a worsening of the ischemia was observed in the affected region due to a phenomenon called "theft" occasioned by the diminished flow due to peripheral vasodilation. Later on a new action mechanism was observed in which some drugs acted on the blood constituents (erythrocytes) by modifying the capacity of these cells to deform, thereby improving perfusion into the tissue. These drugs can be effective in cases of musculoskeletal ischemia when their local/regional use would minimize the undesirable systemic effects.[4]

Pentoxifylline

Pentoxifylline (PTF) was the first drug approved by the FDA (Food and Drug Administration) for the treatment of intermittent claudication. PTF is a derivative of methylxanthine, which acts by inhibiting phosphodiesterase and affects the sanguinary rheology. In other words, it modifies the erythrocyte flexibility, the adhesion and aggregation of the platelets with the consequent reduction of sanguinary viscosity, and improves the blood flow diminishing the fibrinogen and reducing granulocytic function.[5,6]

In 2000, Dorazil-Dudzik et al[7] described an anti-nociceptive action of PTF after intraperitoneal administration in rats and intravenous administration in humans. Owing to the adverse reactions (hypotension, dysrhythmia, agitation, and convulsions) observed in clinical practice after the systemic use of PTF, its local administration appeared to be a therapeutic alternative. Thus, the study showed the local effects of administering 0.5, 1.0, or 2 mg of PTF and 1 or 2 mg of Propentoxifylline (PPTF) injected intraplantarally in rats in order to observe the behavior with the pain induced by formalin. Aside from the antagonism of the hyperalgesia induced by formalin, this study demonstrated biochemical evidence of the inhibition of the synthesis of pro-inflammatory cytokines and phosphodiesterase by PTF and PPTF, emphasizing the local use of these drugs as a valid strategy for the treatment of inflammatory pains.[8]

The microcirculatory dysfunction associated with chronic venous insufficiency (CVI) can be treated by pharmacological intervention, compression therapy, or both. Some drugs such as derivatives of natural products and PTF are very well evaluated in the randomized prospective clinical tests described in the article by Wollina et al. The main microcirculatory effects observed were a reduction in the speed of capillary filtration and an improvement in the levels of the transcutaneous partial pressure of oxygen.[9]

Buflomedil

Buflomedil hydrochloride is a much-used vasoactive drug in peripheral vascular diseases and cerebrovascular insufficiency.[10,11]

Its pharmacodynamic properties include: non-specific inhibition of alpha-adrenoceptors of the smooth blood vessel musculature, inhibition of platelet aggregation, increase in erythrocyte flexibility, non-specific calcium antagonist activity, and anti-hypoxemia activity. The main beneficial property appears to be an improvement of nutritional blood flow in ischemic tissues without producing systemic effects.[4,12]

The oral and parenteral administration of drugs has been studied for the improvement of microvascular perfusion and acceleration of healing. Nonetheless, these methods of administration are accompanied by the risk of adverse reactions or the premature inactivation of the drug by the metabolism of first passage. The encapsulation of medicines in liposomes offers an alternative to the topical release of medications, improving the therapeutic efficacy due to a greater concentration and longer time of the drug on site, in addition to

reducing the systemic effects. [13,14] It has been postulated that liposomes, on crossing the corneal stratum, act as a micro-reservoir for the slow release of medicine. [15,16]

Due to its pharmacological actions on microcirculation, buflomedil encapsulated in liposomes has been studied for topical application in an attempt to improve healing in normal and ischemic skin in tests on rats. These results show a more rapid closing and a complete neovascularization of the injury in animals treated with buflomedil than those treated with liposomes without the active principle, suggesting that this type of local administration of buflomedil could be of great benefit for clinical therapy. [17,18]

Heparin

Heparin is widely used in thrombotic disorders and as an anticoagulant.[19] Its anti-inflammatory effects are also described. In a clinical double-blind test, patients with superficial vein thrombosis (SVT) were subcutaneously treated with heparin of a low molecular weight (sodium enoxaparin). The results of this study showed the tendency of heparin to reduce the incidence of deep vein thrombosis stemming from SVT. Heparin was shown to be effective in reducing the re-incidence and spread of SVT.[20]

In one work, Jones et al used radio-isotope techniques to study the effects of non-fractioned heparin, intra-dermal and intra-venous, in a test of inflammation in guinea pigs induced by cationic proteins, mediators, and antigens. The results showed heparin exerted an anti-inflammatory effect by neutralizing the poly-cationic peptides owing to its anionic charge. It also inhibited the plasmatic exudation induced by poly-L-lysine (PLL) when administered intradermally 60 minutes before the PLL, suggesting that the heparin was not rapidly removed from the injection site.[21]

The intradermal administration of vasoactive drugs is commonly used in mesotherapy for the treatment of chronic pain or degenerative processes such as tendonitis and arthrosis in order to promote a wider passage to the area for blood, and thereby for oxygen. Arterial vasodilators such as buflomedil hydrochloride and peril-heparin are very efficient at minimizing regional hypoxia, and consequently the pain.[22]

Co-dergocrine mesylate

Co-dergocrine mesylate (Hydergine®) is a combination of four dihydro derivatives of ergotoxin and has been used in clinical medicine since 1949 for the treatment of various pathological conditions. It is used in cases of cognitive function loss such as memory and learning and acute cerebrovascular disease. It is even used as a peripheral vasodilator with a beneficial effect on symptoms associated with arterial hypertension. Its action mechanism is related to an alpha-blocker and one possible metabolic function working as a partial agonist or antagonist of the serotonin and dopamine.[4,23]

The topical administration of co-dergocrine mesylate in cream form has been studied in combination with another vasoactive, isosorbide dinitrate, and testosterone in the treatment of age-related erectile dysfunction. In a randomized, double-blind study two creams were tested, one containing the three above-mentioned substances and the other containing only testosterone. The cream containing testosterone and the two vasoactive agents was shown more effective in the studied treatment, possibly owing to the complimentary action of smooth muscle relaxation caused by the dinitrate, and by the blocking action of the co-dergocrine mesylate of the alpha-adrenergic receptors within the cavernous body, causing a dilation of the arteries and arterioles. These results corroborate, suggesting one possible therapy for this dysfunction.[24,25]

Verapamil

Verapamil is a synthetic derivative of papaverine, a prototype of a group of compounds that share the property of selectively inhibiting the flow of calcium ions to the cell through the membrane. Verapamil blocks the calcium channels of the smooth arterial muscle, producing a diminished peripheral resistance and arterial dilation. This medicine is used in arrhythmias, anginas, and hypertension.[1]

The local use of verapamil is being studied as an alternative therapy in the treatment of Peyronie's disease related to erectile dysfunction. Some studies report the intralesional (through injections) and transdermal administration as effective in some symptoms of the disease such as pain, diminution of the curvature, and improvement of erectile capacity.[26,27]

Drugs used in venolymphatic diseases

Venolymphotonic medicines are generally used in disorders such as lymphedema and varicose syndrome.[28,29] The choice of a venotonic drug must be founded on the knowledge of the pharmacodynamics and pharmacokinetics of the molecule, a critical evaluation in clinical studies, the doctor's personal experience, and the cost of the drug.[30,31]

The main objective in using drugs designed to treat vaso-lymphatic disorder is the reduction of edema, which, as stated previously, is responsible for the reduction in the range of movement of joints.

Venolymphotonic drugs can be grouped according to action mechanism (despite various products being associated with the substances of various groups) into: i) phlebotonics; ii) those that increase the reabsorption of a transuded substance; and iii) those that reduce capillary permeability.

Coumarin (Melilotus/_ benzopyrone – increase and reabsorption of transudate)

The melilotus extract has a phyto-complex content aside from other components such as flavonoids, and coumarin, the most active substance in the complex. The generic name of alpha-benzopyrone was adopted to distinguish coumarin from the coumarin derivatives, which are anti-coagulants. Coumarin acts to reduce edema and/or inflammation by increasing venous and lymphatic flow and diminishing capillary permeability and the amount of fluid formed in sub-cutaneous tissue.[4,32,33]

Patches are one type of pharmaceutical widely used in the treatment of localized pathologies such as varicose syndrome and capillary fragility where a prolonged release of the active principle is necessary.[34] In the work done by Minghetti et al, patches containing dried melilotus extract were developed. These were tested in the treatment of localized varicose syndrome as to their capacity to release coumarin and their dermal permeability. The results were adapted for the preparation of potentially useful formulations for local use in the treatment mentioned.[35]

Evaluation of the therapeutic efficacy of a lotion (FLEBS) containing, among other things, *melilotus officinalis*, was done on patients with venous or lymphatic insufficiency. This lotion presented a vasoconstrictive action due to the *Ruscus aculeatus* and was also capable of reducing edema by the action of *melilotus officinalis*. The traditional clinical parameters were evaluated in patients showing improvement of all symptoms monitored, especially edema and pain.[36]

The therapeutic efficacy of *melilotus officinalis* was also evaluated in models of acute inflammation induced with tupertine oil in rabbits. The effects were evaluated by measuring the concentrations of citroline, an *in vitro* test for phagocytosis. *Melilotus officinalis* presented an anti-inflammatory action by reducing the activation of phagocytes in circulation and lowering the citruline production.[37]

Zhao et al[38] studied some extracts of *Melilotus Suaveolens Ledeb* in order to explore their anti-inflammatory mechanisms. Various organic extracts such as ethanol, ethyl acetate, and petroleum ether were tested in an inflammation model and were found capable of considerably inhibiting the production of cytokines and pro-inflammatory mediators – inhibitions comparable to dexamethasone – as well as inducing the release of anti-inflammatory mediators.[39,40]

Rutin and troxerrutin (Flavonoids/g-benzopyrone – phlebotonic

O-(beta-hydroxyethyl)-rutosides (HR), derivatives of rutin, are used in the treatment of chronic venous insufficiency (CVI), a varicose disease and a deep vein disease. Rutin acts to increase venous tone and it is believed to have a "capillary impermeabilization" action by inhibiting hialuronidase.[4,41]

Cesarone et al have studied the effects of HR on microcirculation, resulting in various articles published on prospective, double-blind, randomized, placebo-controlled clinical tests. These works showed good results related to improving venous edema and hypertension with the oral administration of HR (Venoruton).[42-45] The same group recently described a prospective clinical study to evaluate the local efficacy of applying an HR gel on patients with severe CVI and venous microangiopathy. Results showed a significant improvement in microcirculation by an increase in the partial pressure of oxygen and a reduction in local CO_2 pressure.[46]

Troxerutin is a mixture of mono, di, tri and tetrahydroxyethyl-rutosides, flavonoids with an anti-varicose action. A randomized clinical study was made to evaluate the results on edema from a therapy combining coumarin-troxerutin and compression in CVI patients. The results confirmed the reduction of edema, providing an optional treatment for patients who stopped compression therapy after a short time.[47]

In another study, the local effects of troxerutin were evaluated in a topical application in a model of ischemia in skin flaps. The results suggested that troxerutin reduced the ischemia of the skin flap and improved its survival, possibly owing to its anti-edematogenic and anti-oxidant effects and its effects on capillary permeability.[48]

Coumarin-Rutin (increasing transudate reabsorption – phlebotonic)

Laemmel et al[49] developed an *in vivo* model of venous striction in rats and experimentally confirmed the efficacy of a therapy combining coumarin and rutin. This study showed the beneficial effects on microcirculation that the two associated active principles had, whose hemodynamic properties complemented each other explaining the effects on the physio-pathology of veno-lymphatic insufficiency.

The musculoskeletal lesions common to athletes can also be treated by a localized therapy using a mixture of coumarinic bioflavonoids. These promote a rapid reduction in post-traumatic edema allowing an earlier improvement in the range of movement and the pain caused by tissue swelling. Its veno-lymphatonic action diminished capillary permeability assisting the venous and lymphatic return in a very significant way.[22]

Escin (Derived from horse chestnut – phlebotonic)

The derivatives of the *horse chestnut* are widely used in commercial pharmaceuticals. They originate from the plant *Aesculus hippocastanum* which contains some active principles such as esculin, escin, and esculetin. Escin is a triterpenic glicosoid whose therapeutic effects are the inhibition of exudation and edema, aside from increasing vascular permeability.

In a randomized, double-blind clinical study with injured athletes, was investigated the localized action of a gel containing 1% or 2% escin, diethylammonium salycilate, and heparin. The gel containing escin showed excellent safety and efficacy in the treatment of blunt impact injuries.[50,51]

Various clinical trials were carried out to evaluate the local efficacy of a gel containing escin and essential phospholipids in patients with chronic venous hypertension due to CVI, micro-angiopathy, venous ulceration, and superficial thrombophlebitis. All of the works resulted in an improvement of microcirculation, significant diminution of skin temperature, and an elevated O_2 pressure.[52-56]

In another study, the same escin gel was applied to patients with venous hypertension and non-ulcerated varicose veins to evaluate the plasmatic levels of free radicals (PFRs). After treatment, the PFR values diminished to almost normal, indicating improved skin perfusion, which protected it from occasional venous ulceration.[57,58]

Calcium dobesilate/Tribenoside (capillary permeability reducers)

Calcium dobesilate has the capacity to diminish capillary permeability, platelet aggregation, and sanguinary viscosity, aside from the proteolithic effect of the macrophages, where the removal of proteins avoids the formation of fibrosis in chronic edemas. It has been used in the reduction of edema in CVI in diabetic retinopathies, and in hemorrhoidal disease.[59-61]

Various randomized clinical tests have been described emphasizing the use of calcium in patients with CVI.[62,63] In a recent study, the effects of this drug on lymphatic flow and lympho-venous edema were described related to CVI. The dobesilate was able to normalize the lymphatic physiology and improve the symptoms of patients with CVI.[64]

The tribenoside acts to reduce capillary permeability and edema and also antagonizes the endogenic mediators that participate in the painful and inflammatory processes. It is used in venous circulation disorder, phlebitis (adjunctive treatment), hemorrhoids, and varicose syndrome.[4,65]

CONCLUSION

Peripheral vascular diseases (PVDs) constitute a group of diseases that affect the arterial, venous, and lymphatic systems constricting or obstructing the vessels that conduct blood or lymph to the arms and legs, hampering the normal flow. Aside from adopting a healthy lifestyle, the therapy for the PVDs includes the reduction or elimination of risk factors (smoking, obesity, etc.) and the use of vasoactive drugs.

The role of vasomotor disorder is increasingly recognized in the acute and chronic musculoskeletal afflictions, emphasizing the growing need for the use of vasodilating and veno-lymphatic drugs.

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