Clinical pharmacology of venotropics and angyoprotectors, cerebral and peripheral vasodilators, Antimigrane drugs

Chianu Marin
Venous diseases affects 30-50% of the adult population;

Clinical manifestations and severity of these diseases is different: from simple aesthetic embarrassment or failure to intense pain, disability or death instantly.

Diseases occur in the veins of all tissues and organs, but the pathological manifestations more often are the following levels:
Are the following levels:

- **Pelvic veins**: varicose veins, thrombophlebitis;
- **Hemorrhoidal veins**: hemorrhoids thrombophlebitis hemoridala
- **The portal vein**: portal vein thrombosis cavernoma portal hypertension;
- **Cerebral veins**: cavernous sinus thrombophlebitis
Risk factors and its incidence

- Pregnancy and birth - 97%
- Genetic predisposition - 46%
- Surplus weight - 20.6%
- Chronic constipation - 14.5%
- Hormonal contraception - 12.3%

Богачева (2010)
Hyperprogesteronemia

- Diminish of veins smooth muscle tone;
- Reduces excitability of veins;
- Disturb of metabolism in venous wall with degradation of collagen and elastic fibers;
- The massive opening of arterio-venous anastomoses;
- Increased pressure in the subcutaneous and intracutaneous veins of legs;
Hyperestrogenemia

- Produce hypertrophy of internal and media intima of veins;
- Produce endothelial desquamation;
- Increases blood flow in the uterine arteries

Contribute to increase venous eflux in the internal iliac veins producing functional barrier venous outflow from the external iliac veins.
The pathogenesis of venous insufficiency

- **Increase venous pressure**
  - Venodilation
  - Venous valves insufficiency
- **Intravascular venous stasis**
  - Sclerosis of veins and valves
  - Deep vein dilatation, impaired venous outflow and microcirculation
- **Desturb vein permeability**
  - Scleriosis of the skin, subcutaneous tissue, dermatitis, eczema, hyperpigmentation
- **Desturb vesels permeability**
  - Trophic ulcer
Varicose veins of the legs
Trophic ulcers of the leg
Chronic venous insufficiency

Definition

Decompensation stage of venous circulation in legs, with symptoms and clinical signs caused by venous hypertension as a result of structural and functional abnormalities of vein.

A. E. Nicolaides
Chronic venous insufficiency

veins flux in legs
Venoactive drugs: physiological aspects

- Veins, like arteries are innervated by adrenergic system. The veins are alpha (1 and 2) and beta (2) -adrenoreceptor.
  - **Alpha-1-adrenoceptors** are situated on **postsynaptic** membrane of adrenergic endings and are excited by norepinephrine from presynaptic membrane is removed.
  - **Alpha-2-adrenoceptors** are **postsynaptic**, but locate extrasynaptically (lack of sympathetic innervation) and excited by catecholamines from blood (released from the adrenal or administered as prepared).
  - **Alpha-2 adrenoceptors** are the same **presynaptic**, but their exciting inhibits the release of mediators.
  - **Beta-2 adrenoceptors postsynaptic** are located in the intima of the vessels and exciting by the circulating catecholamines dilates the veins.
  - At the same the **beta-2-adrenoceptors** can be **presinaptic** and reduces of mediator release from presynaptic membrane.
Venoactive drugs: physiological aspects

- In tone regulation of veins participate Humor factors. The endogenous substances with vasoconstrictor effect: epinephrine, norepinephrine, angiotensin II, vasopressin, neuropeptide Y, F2-alfa prostaglandin, thromboxane, endothelins.

- Endogenous substances with vasodilator effect: adrenomedulin, acetylcholine, bradykinin, vasoactive intestinal peptide (VIP), histamine, natriuretic peptides (B, C), NO, PGI2, purines (adenosine, ATP).

- dopamine, serotonin, PGE2 and PGD2 can cause both vasoconstriction and vasodilation.
Classification of venotropic or venoactive drugs.

I. The drugs which dilates the veins: 

   A. venodilators:

   - NO donors - nitroglycerine, isosorbide dinitrate, isosorbide mononitrate, molsidomine,
   - alpha-1-adrenoblockers - prazosin, doxazosin, terazosin,
   - Simpatolitics – guanethidine,
II. Arterio- venodilators:

- **NO donors** - sodium nitroprusside,
- **angiotensin converting enzyme** - captopril, enalapril, lisinopril,
- **Angiotensin receptor blockers** - losartan, valzartan, irbezartan,
- **Alpha-2-central adrenomimetics** - moxinidina, guanfacine,
- **Ganglioblockers** - trepriu, azametoniu, trimetaphan,
- **Alpha-1 and 2-adrenoblockers** - phentolamine, tolazoline, phenoxybenzamine,
- **Beta-adrenomimetics** - isoprenaline,
- **Inhibitors of phosphodiesterase** (type III) – milrinone.
Classification of venotrophic or venoactive drugs.

A. venoconstrictors (venotonics):
- **alpha-adrenomimetics** - phenylephrine, etilephrine, Mmidodrine etc.
- **Alkaloids of ergot** - dihydroergotamine, dihidroergotoxine, dihydroergocryptine, vasobral (alpha-dihydroergocryptine + caffeine);
Classification of venotropic or drugs.

B. venoprotectors:
- **rutozides** and their derivatives - routine Troxerutine, venoruton, ascorutina etc.
- **Ginkgo biloba** drugs - extracts from leaves (bilobil, memoplant etc.) and combined (gincor forces etc.)
- **Synthetic drugss** - calcium dobesilat
Classification of venotrophic or drugs.

C. Mixt action drugs (venotonic and venoprotector):
- **Bioflavonoids** - Detralex, diosed-C, diovenor etc.
- **Chestnut fruit** drugs - Escin, escuzan, reparil, venoplant, anavenol etc.
- **Drugs containing Ruscocide** - cyclopropyl-3-phosphate
- **Grape Seed Extract** - endotelon
- **Synthetic drugs** - tribenizid
III. Preparations used for sclerotherapy:
- Decile (trombovar) polidocanol (etoxiscleron)

IV. Used for the prophylaxis and Treatment of venous thrombosis:

a) anticoagulants
   - Direct: heparin nadroparin, enoxaparin, etc.
   - Indirect: warfarin etilbiscumacetat, phenindione etc.

b) fibrinolytic - streptokinase, alteplase, urokinase, nasaruplaza etc.

c) antiplatelets - aspirin, clopidogrel, ticlopidine, dipyridamole, etc.

d) drugs that impruves rheology - pentoxifylline etc.
Bioflavonoids:

Drugs that contain: **diosmin, hesperidin and ascorbic acid - Diosed - C**

The components exert the following action:
- venotonic (venoconstrictoare);
- venoprotector;
- angioprotective;
- antioxidant;
- anti-inflammatory;
- regenerative;
- immunomodulators;
- improvement of rheological properties.
Bioflavonoids: Action venotonic is due to:

- increase the level of norepinephrine synthesized and/or released in the vascular wall to increase contractile capacity of the veins (and primarily small arms) and venous efflux. These contribute to decrease venous stasis and lymph (lymphatic vessels increases peristalsis of lymph draining venous system);

- inhibit the activity of COMT (catechol-O-methyltransferase), an enzyme that inactivates norepinephrine;

- increase contractile protein content (actin) in myocytes veins, which prevents degeneration in vein wall;
Bioflavonoids:
Action venotonic is due to:

- increased sensitivity of contractile proteins of veins to calcium ions and enhances myocyte contractility;
- potentiates the vasoconstrictor effect of adrenaline, noradrenaline also serotonin
- moderately decreased phosphodiesterase activity.
Bioflavonoids:

Venoprotector action is achieved by:

- Prevents or removes aggressive vascular endothelial damage to neutrophils and release of lysosomal enzymes. In stasis also venous hypertension activates neutrophils also monocytes.
- Diminished (Diosmin and hesperidin) the immunoglobulin level (endothelial adhesion molecules responsible for, plus the IVC) responsible for adhesion of leukocytes to the endothelium and for releasing of cytokines, leukotrienes, free radicals, proteolytic enzymes, which help remove microcirculation disorders also trophic changes in tissues.
Bioflavonoids:

Venoprotector action is achieved by (continuation):

- It inhibits hyaluronidase (mostly ascorbic acid), the enzyme that scidează hyaluronic acid, the substance that fortified vascular wall, reducing vascular permeability and stabilization (protection) of vessels;

- Increases the oxygen partial pressure also a decreased carbon dioxide in the tissues removing tissue hypoxia, decrease weight and accumulation of intermediate products of anaerobic processes that cause acidosis.
Bioflavonoids:

Anti-inflammatory action is due to:

- It inhibits the synthesis of prostaglandins (PGE2 etc.) also thromboxane (TrB2), mediators of inflammation by blocking COX-2;

- Reduce the release of inflammatory mediators (PG, leukotrienes);

- Reduces formation of leukotrienes by inhibiting lipooxidării;
Bioflavonoids:

Anti-inflammatory action is due to (continuation)

- Block formation of histamine, serotonin;
- Smaller synthesis of nitroxid synthetase inducible (iNOS) and NO levels decrease;
- Anticomplementary activity manifested by decreasing production of factors that increase the permeability of vessels and stimulates leukocyte migration, factors involved in the early stages of inflammation.
Modificările induse de interacțiunea leucocite-endoteliu sunt prezente din primele momente ale afectării venose.
Reduce adherence, migration and activation of leukocytes with the capillary wall 19,20

Increased capillary resistance also lymphatic drainage 22.23

Inhibits the expression of leukocyte adhesion molecules to vascular endothelium (E-selectin, ICAM-1, VCAM) 21-24

Protecție vasculară optimă prin blocarea interacțiunii leucocite-endoteliu19-24
Protecție optimă la nivel MACRO- și MICROcirculator

SIMPTOME și/sau EDEM

10. Afectare valvulară
11. Reflux venos
12. Vene varicoase

13. Afectare capilară
14. Modificări trofice

15. Ulcer venos

Bioflavonoids:

Antioxidant action is due to:

- Reduction of free radical formation by reducing vascular wall damage;
- Ascorbic acid is a proton donor in oxidation-reduction reactions and forming an endogenous antioxidant system;
- Ascorbic acid provides the activity of other antioxidants in the body (tocopherols etc.)
Bioflavonoids:

Angioprotectoare action is due to:

- Increased synthesis of collagen also elastin
- It inhibits hyaluronidase (mostly ascorbic acid), the enzyme that metabolized hyaluronic acid, the substance that fortifyd vascular wall;
- Reduce the atherogenic lipoprotein (LDL, VLDL) and it increases the anti-atherogenic (HDL) by reducing vascular intima lipid infiltrării.
Bioflavonoids:

Immunomodulatory action is due to:
- Increase nonspecific resistance of body;
- Intensify of activity of immune system cell;
- Increase the release of interferons, antibody synthesis.
Indications of vеноactive drugs

- Primary forms of chronic venous insufficiency (CVI);
- Secondary forms of CVI - consequences incurred vein thrombosis
- Congenital pathology of vein (arteriovenous malformations also dysplasias, hypo- also aplasia main vein);
- Alternative therapy or complex with elastic compression when surgery or sclerosing therapy is contraindicated.
Indications of venoactive drugs

- Pre-also postoperative treatment after surgery CVI
- Prevention also adverse effects of sclerotherapy (hyperpigmentation, phlebitis, inflammation of soft tissues);
- Alternative therapy when is contraindicated in patients compressive therapy (neuropathy, chronic arterial insufficiency) or it can not be supported;
- Prevention of edema when traveling or long flights;
- Acute and chronic varicotromboflebitis.
Indications of venoactive drugs

- Premenstrual syndrome;
- Pelvic pain syndrome;
- Aggravation of varicose veins to when are used contraceptives or onset of menses;
- To stopped CVI symptoms during the pregnancy (quarter 2 and 3);
- Topical forms shown in: acute and chronic symptoms in varicotromboflebitis; postoperative hematoma; cellulite induration; dermatitis, eczema; prevention and treatment of SE of sclerotherapy.
Venoactive drugs: regimen of ussing

- Duration of treatment- minimal 1 month, standard - 3-4 months. Medication can be repeated after 3-4 months (after suspension of treatment effect is maintained for a few months). In advanced cases, particularly trophic ulcers - 6-12 months (duration over 6 months does not increase the incidence of RA).

- **Contraindications:**
  - Hypersensibility, (liver and kidney hard);
  - Lactation and pregnancy (quat 1)
Antiischemic vasodilators drugs

- drugs with vasodilating action prevalent on cerebral vessels, energetic potency of brain, blood rheology, platelets aggregation and antispasmodics with large profile drugs.
Classification

**Miotropics**

1. Vincamimor alcaloids
   - vincamine, vinpocetine,

2. Methylxantines
   - aminophyline, pentoxyphylline, xantinol nicotinate

3. CCB
   - nimodipine, cinarrizine, flunarizine

4. Large profile antispasmodic
   - papaverine, nicoverine, papazole, bencyclane

**Neurotropics**

1. Ergot alkaloids
   - ergotimine, dihydroergotamin, dihydroergotoxine

2. $\alpha$-adrenolytics
   - nicergoline, tolazoline

3. $\beta$-AM
   - izoxuprine, bufenine, bametane

4. Serotoninoblockercs
   - cinarrizine, naftidrofuril, ciproheptadine, lizuride
Drugs used in the complex treatment of cerebral and peripheral circulation disorders

- **Cerebral metabolism**
  1. **Nootropics**
     - piracetam, piritinol, GABA, medophenoxat
  2. **Various drugs**
     - instenon, tanacan, citicoline, orocetam cerebrolyzine,
  3. **Combinated drugs**
     - phezam

- **D influence cuagulabiliy**
  1. **Anticuagulants**
     - **direct**- heparine, nadroparine, enoxaparine, bivaluridine,
     - **indirect**- acenocumarol, warfarin, fenindione,
  2. **Antiaaggregants**
     - acetylsalicylic ac., alprostadil, ticlopidine, sulotroban
  3. **Fibrinolytics** - alteplase, urokinase
Antimigrane drugs

Tipuri de cefalee (durere de cap)

**Sinuzita:**
- de obicei este o durere frontală sau la nivelul naselor fetei

**Cluster:**
- durere în jurul unui ochi sau a unui gât

**Tensiune:**
- durerea este de la gât și la nuine
- este asociată cu tensiunea capului

**Migrena:**
- este tipul de cefalee care este asociat cu senzațiile vizuale și auditive
Migraine is a primary headache, headache is not caused by another disease.

Migraine can be secondary headache that develops as a result of certain diseases (brain tumors, cerebral vessels aneurysms of, hemorrhage subarhnoidian etc.) refers to headache.

Migraine access is characterized by typical symptoms:
- Location of pain in a half-head - hemicrania;
- Pulsating pain;
- Enhancing the exercise;
- Concomitant presence of nausea and / or vomiting;
- Hypersensitivity to light and noise.
Access of migraine is characterized by a sequence of steps and symptoms:

- **Phase I** - extra- and intracranial artery spasm, especially the intracerebral and retina caused by increasing levels of serotonin in the blood with aura development.
Phase II

- dilation of arteries, arterioles, veins, venules also arteriovenous anastomoses, particularly in regions meningiale, temporal, occipital aretrei the external carotid;

- Vasodilation pulsatile and pain caused by reduced levels of serotonin;

- decrease tone extracranial, especially external temporal artery blood flow that lead to marked, stasis especially in meningiale vessels;
Phase III - periarterial tissue edema also vascular wall stiffness vessels and the development of dull pain;

Phase IV - reverse the pathological changes involution.
Pharmacotherapy of migraine

1) jugular access
2) Prophylaxis accesses.
Migraine treatment

- Serotonin agonists – sumatriptane,
- Analgezics - paracetamol, acetylsalicylic acid,
- Ergot alkaloids – ergotamine, dihydroergotamine,
- Methylxantines – caffeine,
- Serotonin blockers – ciproheptadine, divascan, lizurid, sandomigrane,
- Izotiumone derivatives – ravimig,
- B-adrenoblockers - metoprolol, atenolol,
- BCC – nimodipine, cinarizine, flunarizine,
- Antidepressants - amitriptyline, doxepine,
- Combinated drugs – cafergot, vasobral.
Treatments under study

- 25 U botulinum toxin A
- Candesartan
- Zonisamide,
- Tizanidine
- Olazapina
- Neuroactive steroids (ganaxolona)
- Octreotide,
- Inhibitors of nitric oxide synthase (546C88)
- Aspirin 600-900 mg up to 4 times daily
Level I:

Non-opioid analgesics with or without antiemetics drug; Analgesic doses are higher than standards because is present of gastroparesis in migraine; Using forms with rapid release and not those Prolong. Use as early as possible when absorption is not diminished be gastroparesis

Analgesics recommended for jugular access:
- Acetylsalicylic acid 600-900 mg up to 4 times daily or
- Ibuprofen 400-600 mg up to 4 times daily or
- Naproxen 750-825 mg, 250-275 mg then repeated up to 2 sockets or
- 50-100 mg diclofenac (up to 200 mg /day.
Preferred examples of unwanted or therapy.

- When the alarm can be assigned a beta-blocker or a tricyclic antidepressant with anxiolytic effect.
- Coronary heart disease shows beta-blockers and calcium channel blockers.
- In depression shown tricyclic antidepressants or monoamine oxidase inhibitors.
- Shown anticonvulsants in epilepsy, tricyclic antidepressants are not use.
- In hypertension shown beta-blockers and calcium channel blockers.
Preferred examples of unwanted or therapy.

- In Raynaud's disease shows calcium channel blockers, beta-blockers are contraindicated.
- In mitral valve prolapse avoid use of beta-blockers.
- In ischemic stroke in history prescribe aspirin NSAIDs.
- In chronic cerebral ischemia (vascular encephalopathy) shows calcium channel blockers.
Thanks for attention