EVIDENCE BASED STATEMENT

DOMAIN 8, Statement 11

TOPIC: "DOSING AND TIMING OF VALIDATED VENOUS ACTIVE DRUGS TREATMENT"

SEARCH TERMS & SOURCES

("venous insufficiency/drug therapy"[MeSH Terms]) AND (dose OR duration) //PubMed, Embase and Cochrane Library

INCLUSION CRITERIA

Indexed Journal, English Language, lower limb

Reviews, <10 y.

SEARCH RESULT BEFORE - AFTER SELECTION

35 (before) - 0 (after selection)

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Gavrilov SG, Karalkin AV, Moskalenko YP, Grishenkova AS. Efficacy of two micronized purified flavonoid fraction dosing regimens in the pelvic venous pain relief. Int Angiol. 2021 Jun;40(3):180-186.
2. Gonzalez-Ochoa AJ, Raffetto JD, Hernández AG, et al. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial. Thromb Haemost. 2021 Jul;121(7):944-954.
3. Kirienko A, Radak D. Clinical acceptability study of once-daily versus twice-daily micronized purified flavonoid fraction in patients with symptomatic chronic venous disease: a randomized controlled trial. Int Angiol. 2016 Aug;35(4):399-405.
4. Andreozzi GM, Bignamini AA, Davì G, et al. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Circulation. 2015 Nov 17;132(20):1891-7.
5. Falanga V, Fujitani RM, Diaz C, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. Wound Repair Regen. 1999
6. Saviano M, Maleti O, Liguori L. Double-blind, double-dummy, randomized, multi-centre clinical assessment of the efficacy, tolerability and dose-effect relationship of sulodexide in chronic venous insufficiency. Curr Med Res Opin. 1993;13(2):96-108

EVIDENCE BASED STATEMENT

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IDENTIFIED REFERENCES

(from the most recent down)

1. none

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 11, TOPIC: "DOSING AND TIMING OF VALIDATED VENOUS ACTIVE DRUGS TREATMENT"

Validated venous active drugs (VAD) demonstrated significant potentials in chronic venous disease (CVD) signs and symptoms management. The different mechanism of action of the different VAD makes a uniformed posology and prescription timing impossible. Yet, even for the same drug, evidence-based indications on dose adjustments, for example based on hemodynamics and/or personal characteristics such as the patient weight, are missing. At the same time, the duration of the treatment is usually suggested for some months, but without clear specifics, ranging from 1 to 24 months. Preliminary data showed the potential benefit of a dose adjustment of only some drugs.

MPFF demonstrated a benefit in doubling the dose in case of pelvic venous disorders. This approach led to a better pain and blood pooling control compared to the single dose approach.

[**Gavrilov SG, Karalkin AV, Moskalenko YP, Grishenkova AS. Efficacy of two micronized purified flavonoid fraction dosing regimens in the pelvic venous pain relief. Int Angiol. 2021 Jun;40(3):180-186**].

MPFF dose-dependent effect was reported already back in 1987, but in a French written article.

[**Amiel M, Barbe R, Revel D. Etude de la relation dose/effect de Daflon 500 mg par pléthysmographie chez l'homme [in French].** ***J Int Med*****. 1987;88:19-21**]

In 1993, Sulodexide increasing dosages were already successfully associated with an improvement of the venous hypertension related symptoms and signs, including leg oedema.

[**Saviano M, Maleti O, Liguori L. Double-blind, double-dummy, randomized, multi-centre clinical assessment of the efficacy, tolerability and dose-effect relationship of sulodexide in chronic venous insufficiency. Curr Med Res Opin. 1993;13(2):96-108**]

No significant benefits were reported in increasing rutosides dose for CVD treatment.

[**Rehn D, Brunnauer H, Diebschlag W, Lehmacher W. Investigation of the therapeutic equivalence of different galenical preparations of O-(beta-hydroxyethyl)-rutosides following multiple dose peroral administration. Arzneimittelforschung. 1996 May;46(5):488-92**].

Similarly, in a 2004 review, no significant differences were identified in 1000 mg vs 1500 mg per day in calcium dobesilate use for CVD management.

[**Ciapponi A, Laffaire E, Roqué M. Calcium dobesilate for chronic venous insufficiency: a systematic review. Angiology. 2004 Mar-Apr;55(2):147-54**].

Pentoxifylline showed a benefit in some CVD symptoms and in venous wound healing, but with no significant differences between 1000 vs 1500 mg dosage for ulcer healing.

[**Falanga V, Fujitani RM, Diaz C, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. Wound Repair Regen. 1999 Jul-Aug;7(4):208-13**].

Further adequately powered trials are needed to assess the eventually needed adjustments of dosing and prescription timing of the different venous active drugs.

EVIDENCE BASED STATEMENT

Domain 8; Statement 11

STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 11

"The duration protocol of the above report substances intake must follow the single case prescription of the expert physician, taking into account the drug registration documents"

SELECTED REFEREENCES

1. Gavrilov SG, Karalkin AV, Moskalenko YP, Grishenkova AS. Efficacy of two micronized purified flavonoid fraction dosing regimens in the pelvic venous pain relief. Int Angiol. 2021 Jun;40(3):180-186
2. Amiel M, Barbe R, Revel D. Etude de la relation dose/effect de Daflon 500 mg par pléthysmographie chez l'homme [in French]. *J Int Med*. 1987;88:19-21
3. Saviano M, Maleti O, Liguori L. Double-blind, double-dummy, randomized, multi-centre clinical assessment of the efficacy, tolerability and dose-effect relationship of sulodexide in chronic venous insufficiency. Curr Med Res Opin. 1993;13(2):96-108
4. Rehn D, Brunnauer H, Diebschlag W, Lehmacher W. Investigation of the therapeutic equivalence of different galenical preparations of O-(beta-hydroxyethyl)-rutosides following multiple dose peroral administration. Arzneimittelforschung. 1996 May;46(5):488-92
5. Ciapponi A, Laffaire E, Roqué M. Calcium dobesilate for chronic venous insufficiency: a systematic review. Angiology. 2004 Mar-Apr;55(2):147-54
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identified LITERATURE BIAS

Lack of homogenous outcome measure and heterogenous study populations

SUGGESTED NEXT LINES OF RESEARCH

Comparison of different dosage and prescription timing regimens.