

Initial Results of Oral Thrombolytic Agent Clinical Application [†]

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Abstract: At the moment, there is no oral thrombolytic drug on the world pharmaceutical market. The drug Trombovazim, which has a thrombolytic effect under oral administration, has been registered in Russia. It differs from all thrombolytics—it has a fundamentally different mechanism of action. It is not an activator of plasminogen. It independently dissolves a thrombus. It is a direct thrombolytic. The article presents the materials of the initial studies of the drug Trombovazim.

Keywords: thrombosis of the venous system; thrombolytic therapy; oral thrombolytic

1. Introduction

Standard therapy for deep vein thrombosis of the lower extremities includes anticoagulants and antiaggregants, such as bacterial plasminogen activators (streptokinase, staphylokinase), tissue plasminogen activators (alteplase, tenecteplase, purolase, urokinase, etc.), plasmin (human—fibrinolysin, and in project genetic engineered). Dangerous complications seriously limit the use of thrombolytic plasminogen activators. We have developed an oral thrombolytic Trombovazim, which is exogenous thrombolytic proteinase (subtilisin), immobilized on polyethylene glycol, and present the main results of the study on the efficacy and safety of lower limbs deep vein thrombosis treatment with the inclusion of this thrombolytic in therapy.

2. Objective

The objective of this study is to analyze the efficacy and safety of lower limbs deep vein thrombosis treatment with the inclusion of an oral thrombolytic drug based on immobilized subtilisin (Trombovazim[®]) in therapy.

Study tasks:

1. Evaluation of the thrombolytic effect of 3 different drug doses after a 12-day course of treatment of patients with a visualized thrombus of lower limbs deep vein.
2. Evaluation of the revascularization in the zone of compromised blood flow after course of treatment with three different doses of the drug.
3. Determination of the most effective drug dose.
4. Assessment of the drug tolerance and safety.

3. Methods

A multicenter, randomized, double-blind, placebo-controlled clinical trial.

154 volunteers participated in the clinical trial «VETTER-1». All of them received only conservative standard therapy, including anticoagulants (low molecular weight heparins, unfractionated heparins, vitamin K antagonists), nonsteroidal anti-inflammatory drugs and phlebotrophic drugs. None of the participants underwent surgical intervention. The mode of mechanical compression was not taken into account.

All participants were divided into 2 groups—control ($n = 59$) and observation ($n = 95$) group. The control group received a placebo in the form of tested drug with an inactivated substance. The observation group was divided into 3 subgroups consisting of 28, 32 and 35 participants who received tested drug at a dose of 1600, 3200 and 4800 U/day, respectively. The groups were comparable of analyzed characteristics: age, anthropometric statistics, gender, number of days from the disease, localization of thrombus (tibia, femur, tibia + femur), number of visualized thrombus, and laboratory analysis data before initiation of therapy.

The drug effectiveness was determined by means of an objective control method—blood flow ultrasound angioscanning, which reveals presence of a thrombus in thrombosed vein and completeness of revascularization. Statistical treatment of the results was carried out after trial completion.

4. Results

Comparison of revascularization in the zone of compromised blood flow revealed a distinct dose-dependent effect: subgroups that received drug at a dose of 1600, 3200 and 4800 U/day showed a relative frequency of positive dynamics of 0.7070 ($p = 0.0535$, $n = 28$), 0.7257 ($p = 0.0188$, $n = 32$) and 0.7470 ($p = 0.0082$, $n = 35$) respectively, that clearly indicate an increase in the effectiveness of therapy by 21%, 24% and 28% (respectively). The study did not reveal any negative dynamics in the observation group, and recorded 3 such cases in the control group. The difference between frequency of thrombus lysis in the observation group was 0.87 versus 0.63 in the control group, but was statistically unreliable ($p = 0.07$). It should be noted that all participants who received tested drug at a dose of 4800 U/day had complete dissolution of thrombus. The safety assessment was based on the analysis of vital functions, laboratory and instrumental examination of subgroup receiving the maximum drug dosage, and did not reveal any undesirable events at all visits during trials.

5. Discussion

Lower limbs veins thrombosis is a known and widespread problem. All drugs used in standard therapy affect the hemostatic system and have serious side effects. Trombovazim is only existed oral thrombolytic in the world for the time being. An active element of this medicine is an enzyme subtilyzin. It is not a plasminogen activator or plasmin, in fact, it is a proteinase—subtilyzin with a direct fibrinolytic action. Trombovazim is an oral thrombolytic because its subtilisin is immobilized on the polymer by means of unique electron-beam technology (axis-technology), which is described in detail in [1]. In short, the chemical side of this process is that the electron stream creates radical groups on the polymer, and the active group of the polymer is absorbed on the enzyme. As a result, an enzyme globule is covered with a polymer-clad shell. But an active enzyme site functions thoroughly. Axis-technology provides high enteral absorption and bioavailability at the rate of 18% [2].

The direct thrombolytic effect has been proven in vitro. There were taken a blood sampling from the animals' caudal veins into Eppendorf test-tubes, where blood clot formations were for two and twenty-four hours. The formed blood clots with a mass of 0.4 g were separated from the plasma and removed to a glass container connected to a perfusomate. The weight of a fresh 2-h blood clot has decreased in 8 times for the period of 90 min, The weight of an old 24-h blood clot has also decreased in 8 times for the period of two hours [3] (Figures 1 and 2). It is important that the dissolution of the thrombus was done layer by layer, without detachment of pieces of the thrombus.

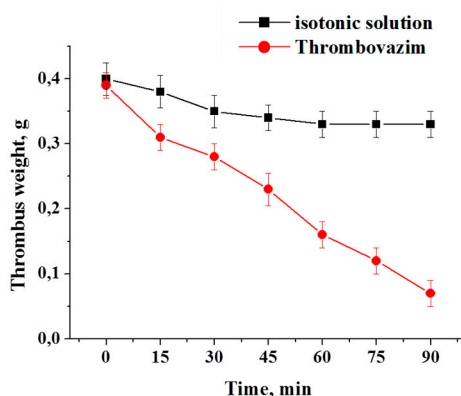


Figure 1. Dissolution of a 2-h thrombus.

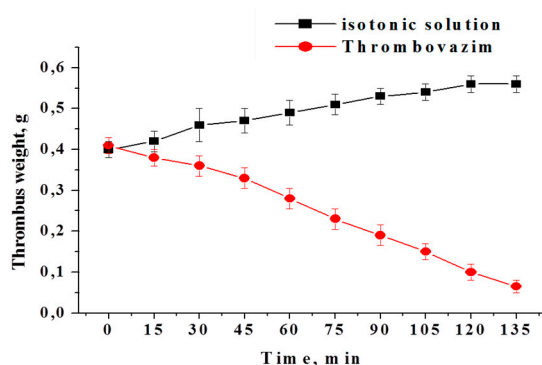


Figure 2. Dissolution of a 24-h thrombus.

A rat model of caudal veins thrombosis induced by k-carraginan showed that manifest thrombosis occurs in 12 h after the injection. Thrombosis has been eliminated in 36 h after the administration of Trombovazim per os [3] (Figure 3).

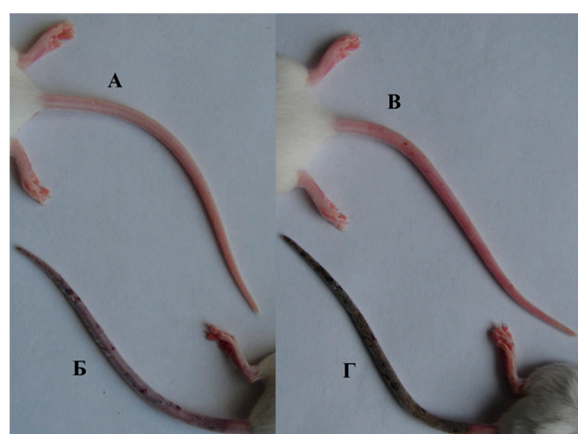


Figure 3. The rat model of tail veins thrombosis, induced by k-carraginan: A. Intact animals; B. Animals 12 h after subcutaneous administration of k-carraginan; B. Animals after 36 h after oral administration of Trombovazim; Γ. Animals without treatment, after 36 h.

All these promising results gave hope that the drug will be effective in humans. Multicenter, randomized, placebo-controlled, double-blind clinical trial of the drug Trombovazim “Therapy of venous thrombosis VETTER-1” confirmed these assumptions. This is the first clinical research of the deep thrombosis of the lower extremities. The study was conducted for 3.5 years and 154 volunteers took part in the trial—men and women aged 35 to 75 years, with the presence of venous thrombosis in the lower extremities. All thrombosis was confirmed by ultrasound with duplex blood flow

scanning. Duration of a disease: midsegment is 7 days, interquartile range—from 5 to 12–13 days, range—from 2 to 37 days. There were 2 patient groups: placebo and study. Everybody was cured with a standard anticoagulant therapy, and in the study group, patients additionally received three doses of Trombovazim: 1600, 3200, 4800 units per day.

The main criterion of efficiency was the bloodstream recovery, recanalization, lysis of the floating part of the clot, bloodstream increase more than 5%. Effectiveness evaluation was conducted on 10th day of therapy. Studies have shown that standard anticoagulation therapy is efficient in a half of the episodes, while taking Trombovazim in a dose of 4800 units per day to ensure the effectiveness of thrombolysis in 75% of episodes. A lysis of the floating part of the clot has been detected with a Trombovazim dose of 4800 units per day in all episodes, but it is not statistically reliable by reason of a small sample.

A pilot study of the efficacy of Trombovazim in the treatment of venous sinus thrombosis (unpublished data) also confirmed the efficacy of Trombovazim: when receiving a Trombovazim at a dose of 2400 units per day for 14 days in patients with tomographically visualized thrombus of venous sinus in 69% of cases there is no thrombus, in 46%—there is a complete restoration of blood flow, and in 54%—there is an increase in blood flow through the reduction of thrombus.

6. Conclusions

The use of the oral thrombolytic agent at a dose of 3200 and 4800 U/day statistically significantly increases the effectiveness of lower limbs deep vein thrombosis treatment. The tested drug doses does not cause hemorrhagic complications and is well tolerated by patients. Analysis of the efficacy and safety of 3 different doses allows to consider 4800 U/day the optimal dosage.

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