# Investigations of effects of orally active peptide and glycoside type antithrombotics

Ph. D. Thesis


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# INTRODUCTION

The objective of the hemostatic system is to preserve the intravascular integrity by achieving a balance between fibrinolysis and thrombosis.

Three major pathways are involved in the hemostasis, like: 1. endothelial cells, 2. platelets, 3. coefficients of coagulation (clotting factors, natural anticoagulants and fibrinolytic system). As factor 4. the circumstances of blood flow (stasis, shear) play also important role in the thrombus development.

Thromboembolic disorders are the major cause of morbidity and mortality in the Western world. For example, in USA twice as many patients die in thromboembolic complication annually than in malignant diseases.

Whereas arterial thrombosis is the most common cause of myocardial infarction, stroke, limb gangrene, and venous thrombosis may lead to pulmonary embolism, which can be fatal, or to postphlebitic syndrome. The disseminated intravascular coagulation (seen in association with many clinical situations, e.g. sepsis, malignancy) and thrombosis, which could develop in case of extracorporeal circulation, are special forms of thromboembolic disorders.

Anticoagulant drugs play indispensable role in the antithrombotic therapy. Current anticoagulant therapy is limited to three classes of compounds: 1. Heparin and derivative substances (unfractionated heparin, low molecular weight heparin, pentasaccharide); 2. Vitamin K antagonists (acenocoumarol, warfarin and phenprocoumon); 3. Direct thrombin inhibitors (hirudin, relatives of hirudin: hirulog, hirugen and argatroban).

In contrast to group 3, heparin and derivative substances, similar to coumarins, are indirect anticoagulants. Heparins (including pentasaccharide) inhibit thrombin and/or factor X indirectly via a conformational change in antithrombin (natural anticoagulant). Antithrombin inhibits mainly the later reactions, while tissue factor pathway inhibitor (TFPI) is a potent inhibitor of the initial phase of coagulation. TFPI directly inhibits factor Xa and then the TFPI/Xa complex inhibits the factor VIIa/TF complex. TFPI can be released upon application of unfractionated heparin and low molecular weight heparin. The TFPI release plays an important role in antithrombotic effect of these compounds.

Gammacarboxy glutamic acid is essential for binding of coagulation factors to the activated platelet membrane. Vitamin K is essential to the synthesis of gamma-carboxy glutamic acid in the liver. By coumarins - as vitamin K antagonist - this synthesis is inhibited, which results in non-functional coagulation factors.

Although the currently available therapies can reduce the risk of thromboembolic events, their use have many limitations. For example, heparins may provoke bleeding, and similarly to direct thrombin inhibitors, because of parenteral application mode, unsuitable for chronic treatment. The oral vitamin K antagonists remain the drugs of choice for long-duration anticoagulation, despite their narrow therapeutic index and numerous food and drug interactions. Additionally, coumarins may cause congenital defects of the fetus when administered during pregnancy. Further drawback is that treatment has to be monitored closely.

The above mentioned facts motivated the initiation of a research program in Drug Research Institute. Our goal was to develop a well-tolerated, novel oral antithrombotic agent with wide therapeutic window for long term treatment. Peptide and glycoside type compounds were investigated in our research program.

## AIM OF EXAMINATIONS

- Demonstration of per os activity of test materials on different species to select the most suitable compound for per os treatment.
- Recognition of in vivo pharmacokinetic properties of effects of compound, and clarification of dose-effect correlations.
- Clarification or support of mode of action.
- Comparison of antithrombotic effect in experimental animal models of thrombosis (deep vein thrombosis model, arterio-venous shunt model, arterial thrombosis model, disseminated intravascular coagulation model). The aim of these studies was the determination of the potential field of indication.

- The aim of “food effect“ examinations were to define the pharmacological bioavailability of test materials in fasted and non-fasted animals. Our further aim was the clarification, whether this effect is species dependent or not.
- Investigation of possible side effects by determination of bleeding time and blood cells count.

At the same time, we wish to provide data with these examinations for possible clinical application.

# MATERIALS AND METHODS

## Experimental animals

- Male SPRD rats (250-350g) (Charles River Hungary Kft).
- Male New Zealand white rabbits (2.5-3.0 kg) (Lab-nyúl Kft)
- Male California rabbits (2.5-3.0 kg) (Lab-nyúl Kft)

## Materials

***At examination of Peptides:***

Melagatran (thrombin inhibitor of Astra-Zeneca), GYKI-14766 (D-MePhe-Pro-Arg-H, Efegatran), GYKI-66131 (D-Hma-Pro-Arg-H), GYKI-66323 (D-cHga-Pro-Arg-H), as well as GYKI-66319 (Eoc-D-Cba-Pro-Arg-H) (Drug Research Institute: DRI) was applied after analytical control. Compounds were stored on 4-6$^{o}$C. Before treatment drugs were dissolved in saline (Salsol A infusion HUMAN Pharmaceutical Works). In the comparative studies the applied doses were: 2.5, 5.0, 10, 15 and 100 mg/kg per os.

***At examination of glycosides:***

Beciparcil (Fournier Co), UF Heparin (25000 IU/5 ml) (Gedeon Richter Chemical Works), Warfarin (Barr Laboratories Inc.), Aspirin (Sanofi-Synthélabo Rt.) Efegatran, GYKI-39484 (4 - nitrophenil - 1,5 - dithio - 3 - azido -3 - dezoxi - β - D -xilopyranoside), GYKI-39521 [4$^{'}$- (methylthio - iminomethyl) - phenyl 1,5 - dithio - β - D - xylopyranoside hidroiodide] as well as the GYKI-39541 (4$^{'}$-nitrophenyl-1,5-dithio-β-D-

arabino-pyranoside) (DRI) were applied after analytical control. Compounds were stored on 4-6$^{o}$C. In the comparative studies the applied doses were: 1.0, 2.0, 4.0, 12.5, 25, 50 and 100 mg/kg per os.

The coagulation was prevented by 3.8 % trinatrium citrate solution (REANAL Rt.) and the animals were anaesthetised by Nembutal (CEVA-Phylaxia Zrt.) in both groups of experiments.

## Methods

*At examination of Peptides*

**Investigation of coagulation parameters:**

Whole blood clotting time (WBCT)

Activated partial thromboplastin time (APTT)

Thrombin time (TT)

**Examination of thrombin induced platelet aggregation (IPA)**

**Thrombosis models:**

Deep vein thrombosis model

Arterial thrombosis model

Arterio-venous shunt model

**Determination of bleeding time**

**Determination of platelet count (Plt)**

**"Food effect" examinations**

*At examination of glycosides:*

**Investigation of coagulation parameters:**

Activated partial thromboplastin time (APTT)

Thrombin time (TT)

Sensitive Thrombin time (sTT)

Protrombin time (PT)

Diluted protrombin time (dPT)

Heptest (Hep)

**Tissue factor pathway inhibitor (TFPI)**

**Thrombosis models:**

Deep vein thrombosis model,

Arterial thrombosis model

Arterio-venous shunt model

Disseminated intravascular coagulation model (DIC)

Determination of fibrinogen level (Fbg)

Examination of fibrinolysis (DWBCL)

Investigation of fibrin degradation products (FDP)

Determination of platelet count (Plt) and leukocyte counts (WBC)

**Determination of bleeding time**

**"Food effect" examinations**

***Description of methods:***

**WBCT assay**

Blood sample (0.36 ml) was taken into the cuvette of thrombelastograph (Haemoscope) and the clotting time was recorded.

**APTT assay**

The APTT was performed using Schnittger-Gross 410 A4 MD automated coagulometer. To 0.1 ml of platelet poor plasma (PPP) 0.1 ml of Rea-clot APTT reagent (Reanal Rt) was added, then after 2 min incubation period 0.1 ml of calcium chloride (0.025 mol/l) started the coagulation process.

**TT assay**

The TT was performed using Schnittger-Gross 410 A4 MD automated coagulometer. 0.1 ml of thrombin (*10* NIH U/ml, bovin, Sigma-Aldrich Co.) solution was added to 0.2 ml of PPP to induce clotting.

**sTT assay**

The TT was performed using Schnittger-Gross 410 A4 MD automated coagulometer. 0.1 ml of thrombin (*5* NIH U/ml, bovin, Sigma-Aldrich Co) solution was added to 0.2 ml of PPP to induce clotting.

**PT assay**

The PT was performed using Schnittger-Gross 410 A4 MD automated coagulometer. 0.2 ml of PT reagent (Simplastin Excel S, Organon Technika) was added to 0.1 ml of PPP and the clotting time was recorded.

**dPT assay**

The dPT was performed using Schnittger-Gross 410 A4 MD automated coagulometer. To 0.2 ml PPP 0.1 ml diluted prothrombin reagent (diluted to 15000 times by 25 mM $CaCl_2$: Thromborel S, Behringwerke AG) was added and the clotting time was recorded.

**Heptest assay**

The Heptest was performed using Schnittger-Gross 410 A4 MD automated coagulometer. To 0.1 ml of PPP 0.1 ml of Heptest/Factor Xa (bovin) reagent was added and after 2 min incubation period 0.1 ml of Heptes/Recalmix solution (Heptest, Haemachem Inc.) to start the coagulation process.

**Investigation of IPA**

The citrated blood samples (0.45 ml) were diluted with saline (0.45 ml). The assays were performed in Whole Blood Aggregometer (Chrono-Log Mod 540 VF). The process was induced by 0.05 ml of thrombin (10 U/ml, bovin Sigma-Aldrich Co.) and was measured by impedance method.

**Investigation of TFPI**

The blood was kept at 56°C for 10 min. TFPI level was determined spectrophotometrically by two-stage chromogenic method. To 20 µl PPP 0.2 ml combined reagent [Thromborel S (TF + phospholipid), Behringwerke AG, FVIIa Enzyme Res. Labs., FX Enzyme Res. Labs., $CaCl_2$] was added. After 10 min incubation, to 100 µl reaction mixture, 50 µl FX and 0.1 ml 2.7 mM substrate was given. The reaction was stopped by 50µl of 50% acetic acid. The formed paranitroanilin was measured spectrophotometrically (Elisa Reader El-800, Bio-Tek Instruments Inc). The quantity of TFPI (ng/ml plasma) was calculated from a calibration curve (made from r-TFPI).

**Determination of Fbg**

To 0.1 ml PPP sample 0.2 ml Multifibren U reagent (bovine thrombin 50 IU/ml, Dade Behring Marburg GmbH) was added and the clotting time was measured in Schnittger-Gross 410 A4 MD automated coagulometer. The result was evaluated with a reference curve, which was done with the Fibrinogen Calibrator Kit. Fibrinogen concentration was given in g/L.

**Investigation of DWBCL**

The citrated blood samples were diluted by buffer (0.1 ml blood+0.8 ml Na-phosphate, 0.15M, pH 7.4) and clotted by thrombin solution (100 NIH U/ml). The clots were kept at 37°C for 16 hours. The quantity of haemoglobin in solutions reflected the rate of fibrinolysis. By adding 0.05 ml of lysate to the 0.95 ml of Na-carbonate solution (0.1%), haematin formed from the haemoglobin, which could be measured spectrophotometrically (Elisa Reader Elx800, KC3 program).

**Determination of FDP**

Blood samples were taken into the ACD (1.7 ml blood into the 0.3 ml acidumcitricum-dextrose). 0.1 ml solution of Ristomycine (7.5 mg/ml, REANAL Rt.) was added to 0.4 ml PPP. After 30 min, the turbidity was measured spectrophotometrically (Elisa Reader Elx800, Bio-Tek Instruments Inc). Four degrees of the aggristin precipitation (rate of FDP) were determined on the base of optical density values.

**Investigation of WBC and Plt**

Blood samples (1.8 ml) were taken into the EDTA (0.2 ml). After suitable dilution (100 fold for WBC and 500 fold for PLT) the samples were put into the automatic appliance (Sysmex F-800, Toamedical Electronics Co).

**Deep vein thrombosis model**

In this model (Pescador model) the thrombus development was induced with stasis based on vascular lesion on inferior vena cava in rats. The wet weight of the thrombus was measured. The effect of the compounds were considered to be of "therapeutic value" when the thrombus weight decreased to 50% compared to the control.

**Arterial thrombosis model**

Thrombus formation in the left carotid artery was induced by complete mechanical constriction for inducing vessel wall damage. The thrombotic occlusion was recorded by the decrease in vessel-surface temperature using a thermistor thermometer in contact with the arterial surface. The effect of the compounds were considered to be of "therapeutic value" when the remission of temperature diminution at least 50% compared to the control.

**Arterio-venous shunt model**

Under Pentobarbital anaesthesia the right jugular vein and left carotid artery were exposed and the two ends of the extracorporeal shunt were inserted into them. Into the centre of the tube a cotton thread was secured. The shunt was left in place for 20 min after the extracorporeal circulation was started. The thread was than removed and the wet weight of the thrombus was measured. The effect of the compounds were considered to be of "therapeutic value" when the thrombus weight decreased to 50% compared to the control.

**DIC model**

In our model, disseminated intravascular coagulation was induced in rabbits by two consecutive intravenous bolus injections of endotoxin (80 and 40 μg/kg) from Escherichia coli, (Sigma Chemical Co). Coagulation parameters (prothrombin time, activated partial thromboplastin time, thrombin time), fibrinogen level, fibrin(ogen) degradation product, fibrinolysis, platelet count, leukocyte count as well as tissue factor pathway inhibitor level were measured. (The methods of PT, APTT, TT, Fbg, FDP, DWBCL, Plt, Fvs and TFPI were used as described previously).

**Determination of bleeding time**

The standardized incision of depilated rabbit ear, in areas free from visible vessels was made with a special device “Simplate I“, than the blood was blotted with filter paper wetted by saline at 15 s intervals until no blood stain on filter paper was seen. This time was measured by stopper and was expressed in minute.

**"Food effect" examinations**

The Areas Under the Curves (AUC) of fasted and foddered animals were compared. The pharmacological bioavailabilities were determined with the AUC ratio, which was calculated on the base of relative TT at peptides, and on the base of TFPI level in case of glycosides.

**Statistical methods**

Values are reported as mean ± SEM. A value of $p < 0.05$ was considered as significant. Comparison between the groups was performed with analysis of variance (ANOVA), further comparison was performed with the Scheffé's test. The Areas Under the Curve (AUC) was calculated by integration (Origin program).

## RESULTS AND CONCLUSIONS

***Peptides:***

From test materials (GYKI-66131, -66319, GYKI-66323) the GYKI-66131 seems to be the most suitable for further development, mainly because of the oral bioavailability and the results in thrombosis models.

1. The GYKI-66131 caused therapeutic anticoagulant and antiplatelet effect in both investigated species (rat, rabbit), and surpassed the references in some parameters after per os treatment.
2. All peptides indicated dose dependent effect. The GYKI-66131 suit the clinical requirements on the base the activity and the duration of effect.
3. The anticoagulant and antiplatelet effect of compounds was developed on the base of the thrombin inhibition.
4. The results demonstrated that each peptide induced significant protective effect in venous and arterial system as well as at extracorporeal circulation in the present of foreign surface, which arise the possibility of extensive application.
5. The pharmacological bioavailability of test materials in fasted and non-fasted animals indicated a "structure-dependent species specificity". For this reason more investigations are necessary to predict the "food effect" at clinical situations.

6. The GYKI-66131 did not induce any significant side effect even at provocative dose or at long treatment duration, and did not cause significant changes in bleeding time or in Plt count (the primer haemostasis was not damaged). The GYKI-66131 did not show accumulation during the treatment for a week.

***Glycosides***

From test materials (GYKI-39521, 39484, -39541) the GYKI-39521 and -39541 seems to be the most suitable for further development.

1. Per os activity of glycosides were demonstrated in both investigated species (rat, rabbit).
2. All glycosides indicated dose dependent effect, and the compounds suit the clinical requirements on the base the activity and the duration of effect.
3. The mechanism of action is known only in part. The test materials indicated only weak anticoagulant effect. The glycosides significantly increased the TFPI level in the plasma, both in rats and rabbits. This effect may contribute to their antithrombotic effect.
4. The glycosides induced significant protective effect in all applied thrombosis models, but the efficacy of compounds was different in various models. These results raise also the possibility of different mode of action of test materials.
5. The diminution of pharmacological bioavailability of test materials in foddered animals was "structure-dependent". More investigations are necessary to predict the "food effect" at clinical situations.
6. The results of side effect examination are favourable. The test materials did not cause significant chances in bleeding time or in plt count (the primer haemostasis was not damaged), and did not induced other visible side effects even at provocative dose. Glycosides did not evoke accumulation or diminution in plt count at long time treatment.

Aiming a development of a novel oral antithrombotic agent, two parallel research directions were initiated in Drug Research Institute. In spite of different mode of action and structure of compounds, we were able to find promising drug candidates in both peptide and glycoside groups, but more examinations necessary for drug development.

# PUBLICATIONS

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