Research Article

# Action of an Indolinone Derivative on Plasma Hemostasis

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## Abstract

The action of a new pharmaceutical substance of indolinone series, an sGC inducer with antiplatelet activity, on rat blood plasma hemostasis was studied. It was shown that the antiplatelet substance after single oral administration to rats considerably increases thrombin time after 3 hours (24.5 versus 17.3 in control, p<0.05). Other plasma hemostasis parameters were unchanged.

*Key words:* antiplatelet, indolinone derivative, plasma hemostasis.

## Introduction

Thrombosis plays a key role in the development of acute coronary syndrome, making antiplatelet therapy an important part of prevention and treatment of cardiovascular diseases [1]. One of the main risk factory of cardiovascular disease relapse is insufficiency of existing therapy in people resistant to aspirin and clopidogrel [2,3]. This problem can be solved by using antiplatelet drugs with a novel mechanism of action. Also, increased blood clotting plays a role in cardiovascular complications [4,5]. There were no earlier studies of the action of the indolinone derivative on blood plasma hemostasis.

Study goal – Assess the action of a new antiplatelet compound on rat blood plasma hemostasis after oral administration.

## Materials and Methods

Test article – pharmaceutical substance 2-[2-[(5RS)-5-(hydroxymethyl)-3-methyl-1,3-oxazolidine-2-yliden]-2-cyanoethylidene]-1H-indol-3(2H)-one.

Outbred Wistar rats (n=10) were used as test system. Rat handling was performed in accordance with the European Convention and other regulating documents [6].

Intact blood was sampled from common carotid artery of anesthetized rats. The blood was stabilized with 3.8% solution of sodium citrate in 9:1 (v:v) ratio, blood plasma was produced by centrifuging at 2000 g for 20 min.

Plasma hemostasis was assessed by fibrinogen content, activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and Thrombin Time (TT). These parameters were assessed by KG-4 coagulometer (Cormay, Poland). Fibrinogen content was assessed using Claus method.

The antiplatelet drugs were administered to rats once orally in 10 mg/kg dose. At the end of experiment the animals were sacrificed by $CO_2$.

Statistical analysis was performed by «R» software. The data is presented as mean values and mean standard deviation (M ± m). Significance of difference (p<0.05) between the tests was assessed using Mann–Whitney U test.

## Result and Discussion

No significant changes of main parameters of plasma hemostasis: fibrinogen, aPTT and PT, were found 3 hours after single oral administration of the antiplatelet drug in 10 mg/kg dose. TT was increased by 42% compared to the control group (Table 1).

**Table 1.** Effects of the new antiplatelet drug (10 mg/kg) on rat blood plasma hemostasis.

| Group | Fibrinogen | aPTT | PT | TT |
|---|---|---|---|---|
| Control (n=5) | 2.0±0.1 | 14.8±0.7 | 20.4±0.6 | 17.3±2.3 |
| Antiplatelet drug (n=5) | 1.8±0.1 | 15.2±0.6 | 20.1±0.3 | 24.5±1.0* |

*Note:* * –p < 0.05 compared to control.

The new antiplatelet drug doesn't affect blood plasma fibrinogen content, activated partial thromboplastin time and prothrombin time, but considerably increases the thrombin time, 3 hours after single oral administration in 10 mg/kg dose [7]. The reduction of platelet aggregation by the new drug leads to reduced exit of active components of the coagulation system from the platelets, which may account for the lengthening of thrombin time. There may also be other explanations for this. Additional studies are required for confirmation or discovery of another mechanism, including, possibly, direct inhibition of thrombin.

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