Antithrombin activity of a new triazolopyrimidine derivative

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Abstract.

In the pathogenesis of inflammatory processes caused by viral and bacterial infections, there are various disorders of many systems of the organism, including pathology of hemostasis system characterized by prethrombotic state. According to clinical recommendations, the use of new oral anticoagulants is aimed at reducing the risk of hypercoagulation disorders, that's why the search and study of new direct anticoagulant compounds is relevant. Pyrimidine derivatives have been shown to exhibit various types of pharmacological activity, including anticoagulant activity.

Purpose of the study. Search for anticoagulant compounds among derivatives of triazolo[1,5-a]pyrimidines, study of their mechanism of action and anticoagulant activity without and in conditions of hypercytokinemia.

Objectives of the study.

1. To search for compounds with anticoagulant activity in vitro and in vivo in a number of new condensed derivatives of triazolo[1,5-a]pyrimidines.

Materials and methods.

To study the effect of a new condensed triazolo[1,5-a]pyrimidines derivatives in vitro and in vivo on coagulogram parameters (without and in conditions of hypercytokinemia). All compounds and the comparison drug were studied in the dose range of 100-1 μM to calculate the EC_{50} value. Dabigatran etexilate was studied as a comparison drug. For in vitro studies, the test samples were studied in a dose-dependent manner. In the in vivo test, the most active compounds were chosen.The most active compound (triazolopyrimidine derivative) and the comparison drug were administered to rats once intragastrically at doses of 5.5 mg/kg and 12 mg/kg, respectively, 2 h before the study. Hypercytokinemia was created by lipopolysaccharide by intravenous injection at a dose of 2 mg/kg into the tail vein of the rat. The effect of the tested compound and the comparison drug on blood coagulogram parameters (APTT, TT, PT) in in vitro and in vivo tests was determined chronometrically on a SOLAR hemocoagulometer (Belorussia).

Results.

All studied compounds had showed different activity in coagulometric tests. The greatest change in clotting time was observed in the thrombin time test. It was shown that the tested samples and the comparison drug manifested antithrombin activity comparable in terms of EC_{50} in in vitro test (table 1). Most active triazolopyrimidine derivative in vitro test was compound HC-NAR-0273b the activity of which is comparable to the comparison drug, it was chosen for in vivo studies. Other compounds were less active. All compounds decreased thrombin time in hypercytokinemia, but the most pronounced effect comparable to the comparison drug was shown by the compound HC-NAR-0273b .

In in vivo experiments at a single intragastric administration to rats prolonged thrombin time 5.6 times relative to control values, but was 2 times inferior to the comparison drug dabigatran etexilate (table 2). However, under conditions of hypercytokinemia the tested compound was 1.3 times superior to the comparison drug in antithrombin activity. The new triazolopyrimidine derivative in in vitro and in vivo experiments showed high antithrombin activity in sepsis-mediated conditions causing a systemic inflammatory response, which may make a significant contribution to reducing the risk of thrombosis in viral and bacterial infections.

Table 1. Antithrombin activity of triazolopyrimidine derivatives and comparison drug dabigatran etexilate in normal conditions and under hypercytokinemia conditions (M±m) (n=5)

№	Tested compounds	EC50, μM	EC50, μM In LPS addition
1	HC-NAR-0273b	1.3	0.8
2	KC-786	1.2	2.1
3	KC-G	1.0	4.4
4	FV-174/Na	0.9	4.9
5	Dabigatran etexilate	1.4	0.8

Table 2. Effect of compound HC-NAR-0273b and comparison drug dabigatran etexilate in equimolar doses on rat coagulogram parameters after 2 hours of single intragastric administration under hypercytokinemia conditions (M±m) (n=5)

№	Dose, mg/kg	Tested compounds	Thrombin time, sec	Thrombin time in addition of LPS, sec
1	5,5	HC-NAR-0273b	325,3 ± 7,1	640,3 ± 7,4
2	12,0	Dabigatran etexilate	603,9 ± 18,2	566,1 ± 45,5

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