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Study of the pharmacokinetics of non-immunogenic staphylokinase in patients with acute myocardial infarction and acute ischemic stroke

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The aim. To investigate the pharmacokinetic parameters of non-immunogenic staphylokinase (Fortelyzin®, SuperGene LLC, Russia) in patients with acute myocardial infarction with ST-segment elevation (STEMI) on the electrocardiogram and in patients with ischemic stroke.
Materials and methods. The clinical study was conducted in 50 patients with STEMI after a single intravenous administration of non-immunogenic staphylokinase at a dose of 15 mg and in 50 patients with ischemic stroke after a single intravenous administration of the drug at a dose of 10 mg. The main pharmacokinetic parameters were determined: half-life, initial concentration, volume of distribution, clearance, and area under the pharmacokinetic curve.
Results. As a result of the study of the pharmacokinetics of non-immunogenic staphylokinase, it was found that after a single intravenous administration of the drug at a dose of 15 mg, the initial concentration was 7.1 ± 2.7 μg/mL, the half-life was 5.77 ± 0.72 min, the clearance was 0.33 ± 0.04 l/min, and the area under the pharmacokinetic curve (AUC_{0-t}) was 42.9 ± 3.2 μg/mL*min. After administration of the drug at a dose of 10 mg, the initial concentration was 2.8 ± 0.3 μg/mL, the half-life was 5.11 ± 0.56 min, the clearance was 0.35 ± 0.06 l/min, and the area under the pharmacokinetic curve (AUC_{0-t}) was 28.5 ± 3.6 μg/mL*min. The terminal half-life was 32 min in both dosage regimens.
Conclusion. It was found that non-immunogenic staphylokinase is characterized by a short half-life and high clearance, which ensures the safety of the drug in clinical practice. The peculiarities of the pharmacodynamics of non-immunogenic staphylokinase, associated with its interaction with plasmin in the thrombus and subsequent recirculation of released drug molecules, allow it to be used in low doses, regardless of the patient's body weight, despite the short half-life.

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Keywords: non-immunogenic staphylokinase; pharmacokinetics; thrombolysis; myocardial infarction; ischemic stroke
Abbreviations: MI — myocardial infarction; STEMI — ST-segment elevation myocardial infarction; PE — pulmonary embolism; mRS — modified Rankin scale; TLT — thrombolytic therapy.

Исследование фармакокинетики лекарственного препарата неиммуногенной стафилокиназы у пациентов с острым инфарктом миокарда и ишемическим инсультом

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Цель. Исследовать фармакокинетические параметры неиммуногенной стафилокиназы (Фортелизин®, ООО «СупраГен», Россия) у пациентов с острым инфарктом миокарда с подъёмом сегмента ST (ОИМпST) электрокардиограммы и у пациентов с ишемическим инсультом.

Материалы и методы. Клиническое исследование проведено у 50 пациентов с ОИМпST после однократного внутривенного введения препарата неиммуногенной стафилокиназы в дозе 15 мг и у 50 пациентов с ишемическим инсультом после однократного внутривенного введения препарата в дозе 10 мг. Определялись основные фармакокинетические параметры — период полувыведения, начальная концентрация, объём распределения, клиренс, а также площадь под фармакокинетической кривой.

Результаты. В результате исследования фармакокинетики неиммуногенной стафилокиназы было установлено, что после однократного внутривенного введения препарата в дозе 15 мг начальная концентрация составляла 7,1±2,7 мкг/мл, период полувыведения — 5,77±0,72 мин, клиренс — 0,33±0,04 л/мин, площадь под фармакокинетической кривой (AUC_{0-t}) — 42,9±3,2 мкг/мл*мин. После введения препарата в дозе 10 мг начальная концентрация составляла 2,8±0,3 мкг/мл, период полувыведения — 5,11±0,56 мин, клиренс — 0,35±0,06 л/мин, площадь под фармакокинетической кривой (AUC_{0-t}) — 28,5±3,6 мкг/мл*мин. Терминальный период полувыведения составил 32 мин в обоих вариантах дозирования.

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Заключение. Установлено, что неиммуногенная стафилокиназа характеризуется коротким периодом полувыведения и высоким клиренсом, что обеспечивает безопасность применения препарата в клинической практике. Особенности фармакодинамики неиммуногенной стафилокиназы, связанные с ее взаимодействием с плазмином в толще тромба и последующей рециркуляцией высвобождающихся молекул препарата, позволяют использовать ее в низких дозах независимо от массы тела пациента, несмотря на короткий период полувыведения.
Ключевые слова: неиммуногенная стафилокиназа; фармакокинетика; тромболизис; инфаркт миокарда; ишемический инсульт
Список сокращений: ИМ — инфаркт миокарда; ОИМпST — острый инфаркт миокарда с подъёмом сегмента ST; ТЭЛА — тромбоэмболия легочных артерий; МШР — модифицированная шкала Рэнкина; ТЛТ — тромболитическая терапия.

INTRODUCTION

Thrombolytic therapy (TLT) is a pathogenetically sound method for treating acute myocardial infarction (MI) with ST-segment elevation (STEMI), ischemic stroke, and massive pulmonary embolism (PE), reducing the risk of disability and mortality [1]. TLT is simple to perform, relatively inexpensive, has extensive experience in real clinical practice, and can be used at all stages of care [2]. The introduction of thrombolytic therapy into clinical practice has led to a significant reduction in 30-day mortality in patients with STEMI — from 17–18 to 5–8% [3].

The history of TLT for MI spans more than 60 years. At the Institute of Therapy of the USSR Academy of Medical Sciences (National Medical Research Center of Cardiology named after Academician E.I. Chazov), under the guidance of Academician A.L. Myasnikov, after a large number of experimental studies of fibrinolysin (now understood as plasmin) in thromboses of various localizations, in 1961, E.I. Chazov was the first in the world to use fibrinolysin in a patient with acute MI, followed by heparin therapy [4]. Work on creating effective and safe thrombolytic drugs with a convenient dosing regimen, absence of allergenic properties, and minimal risk of hemorrhagic complications has been carried out in many scientific laboratories. Currently, in the Russian Federation, plasminogen activators (alteplase, tenecteplase, staphylokinase) are most widely used for TLT. It is known that staphylokinase is the most fibrin-selective thrombolytic drug, since it exhibits the highest affinity only to plasminogen adsorbed on a fibrin clot, the so-called γ-plasminogen [5]. Staphylokinase surpasses prourokinase, alteplase, and tenecteplase in its selectivity for fibrin [5]. The plasmin-staphylokinase complex activates the transition of γ-plasminogen to plasmin on the surface of the thrombus. The plasmin formed simultaneously enhances the fibrinolytic activity of staphylokinase, and its excess is rapidly inactivated in the systemic circulation by α2-antiplasmin [6]. The high fibrin selectivity of staphylokinase is confirmed by a minimal decrease in the level of fibrinogen in the blood, on average by 5%, while alteplase causes a drop in the level of fibrinogen to 30% [7]. The absence of systemic fibrinogenolysis explains the high safety of staphylokinase: the risk of bleeding is lower if using other thrombolytics that are non-selective to fibrin.

When the plasmin-staphylokinase complex is inhibited by α2-antiplasmin, an active staphylokinase molecule is released for subsequent recycles. The recirculation of staphylokinase allows reducing the dose used in clinical practice compared to tissue plasminogen activators and makes it independent of the patient's body weight [8]. An expanded kinetic analysis of the reaction of staphylokinase with plasmin showed that its catalytic activity is 1000 times higher than that of alteplase [9].

Unlike the native staphylokinase molecule, three amino acids (Lys74, Glu75, and Arg77) are replaced by alanine in the non-immunogenic molecule, as a result of which the drug does not have antigenic activity [10]. Non-immunogenic staphylokinase is a single-chain molecule with a molecular weight of 15.5 kDa. It has been established that the fibrinolytic activity of non-immunogenic staphylokinase is 40% higher than that of the native staphylokinase molecule [11].

THE AIM. To establish the pharmacokinetic parameters of non-immunogenic staphylokinase in clinical studies in patients with acute myocardial infarction with ST-segment elevation and with ischemic stroke.

MATERIALS AND METHODS

Blood sampling in patients with acute myocardial infarction with ST-segment elevation

A multicenter open randomized comparative study of the efficacy and safety of a single bolus injection of non-immunogenic staphylokinase

(15 mg) and tenecteplase (30–50 mg) in patients with STEMI (FREEDOM-1) based on 11 leading medical institutions in Russia was conducted in the period from October 2014 to August 2016 in accordance with the permission of the Ministry of Health of Russia No. 261 dated May 16, 2014 [12, 13]. Before inclusion in the study, all patients signed an informed consent form. The study was approved by the Ethics Council of the Ministry of Health of Russia (protocol No. 81 dated April 15, 2014) and local Ethics Committees based on research centers.

382 patients were included in the study. Inclusion criteria: diagnosis of STEMI in the first 12 hours from the onset of the disease. *Exclusion criteria*: bleeding, hemorrhagic stroke, ischemic stroke in the preceding 6 months, diseases with an increased risk of bleeding. A complete list of *inclusion* and *exclusion criteria* in the study has been published previously [12, 13]. Criteria for the effectiveness of TLT — the number of patients with a decrease in the ST-segment of the electrocardiogram by 50% from the initial value after 90 min, as well as the number of patients with restoration of coronary blood flow in the infarct-related artery according to TIMI 2 + TIMI 3 (Thrombolysis in Myocardial Infarction) criteria according to coronary angiography. Safety criteria were the number of major bleeding events, intracranial hemorrhages, as well as mortality from all causes, cardiogenic shock, and recurrent myocardial infarction during the hospitalization period.

Patients were randomized into 2 groups (n = 191 each) for the administration of non-immunogenic staphylokinase (Fortelizin®, SuperGene LLC, Russia) or tenecteplase (Metalyse®, Boehringer Ingelheim International, Germany). Randomization was carried out by the method of envelopes. Recombinant non-immunogenic staphylokinase was administered at a dose of 15 mg regardless of body weight as a bolus over 10–15 seconds, tenecteplase — as a bolus at a dose of 30–50 mg depending on body weight, according to the instructions for medical use.

During the clinical study, blood was taken from 50 patients 3, 6, 9, 12, 15, and 20 min after the administration of non-immunogenic staphylokinase in a volume of 2 mL into heparin tubes with the patient's number and study point indicated on the label. The blood tubes were centrifuged using a Liston C 2202 centrifuge for 10 min at a speed of 3000 rpm (Liston, Russia). Blood plasma in a volume of at least 1 mL was transferred to an Eppendorf tube. The choice of study points was based on the results of a preclinical pharmacokinetic study in hamsters, where the half-life was 1.9 min [14].

Blood sampling in patients with ischemic stroke

A multicenter open randomized comparative study of the efficacy and safety of a single bolus injection of non-immunogenic staphylokinase and bolus-infusion administration of alteplase in patients with ischemic stroke (FRIDA) was conducted in the period from March 2017 to March 2019 in accordance with the permission of the Ministry of Health of Russia No. 498 dated July 15, 2016. The study was approved by the Ethics Council of the Ministry of Health of Russia (Protocol No. 125 dated May 24, 2016) and local Ethics Committees based on research centers.

336 patients were included in the study in 19 clinical centers. *Inclusion criteria*: ischemic stroke — no more than 4.5 hours from the onset of symptoms. Exclusion criteria: blood pressure over 185/110 mm Hg, signs of severe stroke (NIHSS stroke scale score >25), active bleeding, hemorrhagic stroke, diseases with an increased risk of bleeding. A complete list of inclusion and exclusion criteria in the study was published previously [15, 16]. The primary efficacy criterion was the number of patients who achieved good functional recovery (0–1 points on the modified Rankin scale [mRS]) at 90 days. Secondary efficacy criteria were the change in the median NIHSS after 24 hours and at 90 days. Safety criteria were mortality from all causes at 90 days, symptomatic hemorrhagic transformation (according to ECASS-III criteria), major bleeding.

Patients were randomized into 2 groups (n = 168 each) for the administration of non-immunogenic staphylokinase (Fortelizin®, SuperGene LLC, Russia) or alteplase (Actilyse®, Boehringer Ingelheim International, Germany). Randomization was carried out by the method of envelopes. Non-immunogenic staphylokinase was administered at a dose of 10 mg regardless of body weight as a bolus over 5–10 seconds, alteplase — as a bolus-infusion at a dose of 0.9 mg/kg (maximum 90 mg) depending on body weight, according to the instructions for medical use.

During the clinical study, blood was taken from 50 patients 3, 6, 9, 12, 15, and 20 min after the administration of non-immunogenic staphylokinase in a volume of 2 mL into a heparin tube with the patient's number and study point indicated on the label. The blood tubes were centrifuged using a Liston C 2202 centrifuge for 10 min at a speed of 3000 rpm (Liston,

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Russia). Blood plasma in a volume of at least 1 mL was transferred to an Eppendorf tube. The choice of study points was also based on the results of a preclinical pharmacokinetic study [14].

Determination of the concentration of non-immunogenic staphylokinase in the blood

To determine the concentration of non-immunogenic staphylokinase in blood plasma, calibration samples were prepared with concentrations of 10; 5; 2.5; 1.25; 0.625; 0.312; 0.156 and 0.078 μg/mL with a buffer solution (20 mM Tris-HCl, 150 mM NaCl, 0.005% Tween-20, pH=8.0) based on literature data on achieving a staphylokinase concentration in the blood of 1.24 ± 0.24 μg/mL after a single administration at a dose of 10 mg [17]. The test samples were diluted 3000 times with a buffer solution. For each sample, 3 wells of a plate with primary mouse antibodies to staphylokinase were allocated. 100 μL of test and calibration samples were added to the wells. 100 μL of buffer solution was added to the negative control wells. The plate was incubated for 60 min at a temperature of 37°C. After incubation, the liquid was removed, and the wells were washed three times with 300 μL of buffer solution. Then, 100 μL of a solution of secondary rabbit antibodies labeled with horseradish peroxidase (20 mM Tris-HCl, 150 mM NaCl, 0.005% Tween-20, pH = 8.0, 2% bovine serum albumin, secondary antibodies diluted 1:1000) was added to each well, and the plate was incubated for 60 min at a temperature of 37°C. After incubation, the liquid was removed from the plate, and the wells were washed five times with 300 μL of buffer solution. Then, 100 μL of substrate solution (150 mM phosphate-citrate buffer, pH = 5.0, 0.07% orthophenylenediamine, 0.06% H_2O_2) was added to each well. Incubated at room temperature for 3–5 min until staining appeared in the negative control sample. 50 μl of stop reagent (10% sulfuric acid solution) was added to each well. Within 15 min after adding the stop reagent, the optical density was measured in each well at 490 nm on a microplate photometer (ImmunoChem-2100, HTI, USA). The average optical density value was calculated in three wells for each sample. The concentration of the drug in the test samples was determined using a calibration curve.

Statistical processing

Sample size calculation

According to the literature, the frequency of achieving the primary efficacy criterion — a decrease in the ST-segment of the electrocardiogram by 50% from the initial level 90 min after thrombolysis — when using tenecteplase is 66% [18], the frequency of achieving the primary efficacy criterion when using non-immunogenic staphylokinase according to a phase II clinical study is 83%. To prove the hypothesis of non-inferiority of non-immunogenic staphylokinase compared to tenecteplase in patients with STEMI, a clinically significant limit of 12.5% was chosen. It was established that a really absent difference between the drugs (the upper limit of the 95% confidence interval [CI] will be lower than the non-inferiority limit) with 80% probability[1] can be detected with a set of 173 patients in each group (n = 347 patients for 2 groups). Taking into account the possible dropout of 10% of patients due to violations of the study protocol, a set of 382 patients is necessary (n = 191 patients in each group). Based on the fact that the study of the pharmacokinetics of the comparison drug tenecteplase was carried out depending on the dose in 20 (50 mg) or 48 (30 mg) patients [19], venous blood was taken from 50 patients to study the pharmacokinetic parameters of non-immunogenic staphylokinase.

To prove the hypothesis of non-inferiority of non-immunogenic staphylokinase compared to alteplase in patients with ischemic stroke, it was established that the frequency of achieving the primary efficacy criterion — the number of patients with good functional recovery at 90 days after thrombolysis (mRS 0–1 points) — according to the SITS-MOST registry is 54.8% [20]. The frequency of achieving the primary efficacy criterion when using placebo averages 37.9% — this value was obtained from the ECASS II [21], Atlantis [22] and ECASS III [23] studies, where the favorable effect when using placebo is 36.6%, 32% and 45.2%, respectively. Thus, the difference between good functional recovery with the use of alteplase and placebo is 16.9%. The non-inferiority limit was set at 16%. When demonstrating at a two-sided significance level of 5% to maintain 80% comparison power, the minimum number of patients included in the study was estimated at 152 patients in each group. Taking into account a possible 10% dropout, the sample size was increased to 336 patients (n = 168 patients in each group). Based on the fact that the study of the pharmacokinetics of the comparison drug alteplase was carried out in 53 patients [19], venous blood was taken from 50 patients to study the pharmacokinetic parameters of non-immunogenic staphylokinase.

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Statistical methods

The pharmacokinetic curve is described by the equation:

$$C(t)=A\times e^{-\alpha t}+B\times e^{-\beta t},$$

where A and B are proportionality coefficients (μg/L); α is the rate constant of drug distribution (1/min); β is the rate constant of terminal elimination (1/min).

The following parameters were calculated: half-distribution period ($t_{1/2\alpha}$), plasma half-life (t1/2β), initial concentration in blood plasma (C_0), volume of distribution (V_1 and V_2), drug clearance (CL_1 and CL_2), area under the pharmacokinetic curve within the duration of observation (AUC_{0-t}), area under the pharmacokinetic curve from zero to infinity ($AUC_{0-\infty}$), area under the curve from zero to ∞ with extrapolation of the final phase (AUMC), mean residence time of the drug in the systemic circulation (MRT), apparent volume of distribution at steady state (V_{ss}).

Statistical analysis was performed using the R program (version 4.2) (The R Foundation for Statistical Computing and Graph Pad Prism 7, Graph Pad Software Inc., USA). For continuous indicators, the following descriptive statistics are presented: number of data excluding gaps (*n*), arithmetic mean (M), standard deviation (SD), median (Me), 25 and 75 percentiles (Q1 and Q3, respectively).

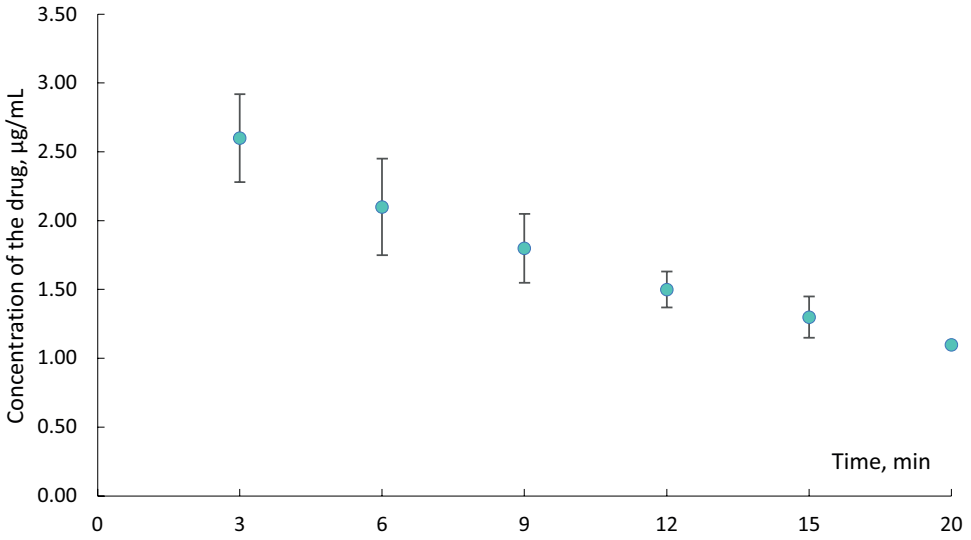

Figure 1 – Pharmacokinetic profile of non-immunogenic staphylokinase at a dose of 15 mg in patients with acute myocardial infarction with ST-segment elevation.

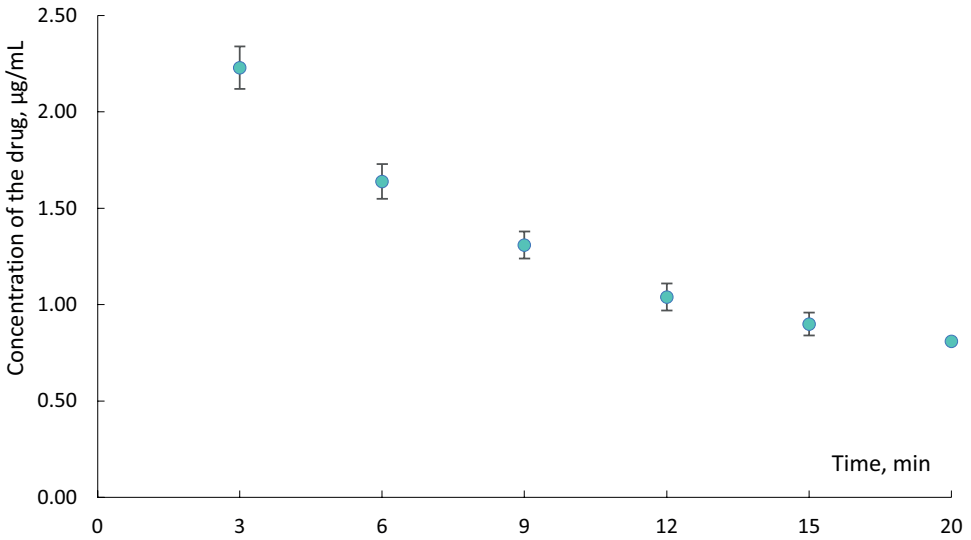

Figure 2 – Pharmacokinetic profile of non-immunogenic staphylokinase at a dose of 10 mg in patients with ischemic stroke.

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Table 1 – Baseline characteristics of patients

Characteristics	Indicator (n = 50)
Gender, male / female, n (%)	38 / 12 (76% / 23%)
Age, M ± SD, years	58.9 ± 9.9
Patients over 75 years old, n (%)	3 (6%)
Weight, Me (Q1; Q3), kg	82 (73; 91)
Body mass index, Me (Q1; Q3), kg/m^2	27.8 (25.3; 31.2)
Arterial hypertension, n (%)	37 (75%)
Dyslipidemia, n (%)	43 (86%)
Smoking, n (%)	20 (40%)
Type II diabetes mellitus, n (%)	7 (14%)
Myocardial infarction, n (%)	6 (12%)
ST-segment elevation, M ± SD, mm	3.58 ± 1.96
SBP, M ± SD, mm Hg	118.6 ± 8.2
DBP, M ± SD, mm Hg	74.7 ± 7.2
HR, M ± SD, bpm	75.9 ± 14.7
STEMI localization, n (%):	
anterior	21 (42%)
inferior	28 (56%)
other	1 (2%)
Time from the onset of symptoms to TLT, M ± SD, h	3.4 ± 1.7

Note: TLT — thrombolytic therapy.

Table 2 – Assessment of the effectiveness and safety of non-immunogenic staphylokinase in patients with acute myocardial infarction with ST-segment elevation

Criterion	Indicator (n = 50), n (%)
Decrease in the ST-segment after 90 minutes by 50%	40 (80%)
Restoration of coronary blood flow according to TIMI criteria:	
0	12 (24%)
1	3 (6%)
2	16 (32%)
3	19 (38%)
2+3	35 (70%)
Death from all causes	1 (2%)
Cardiogenic shock	2 (4%)
Recurrent myocardial infarction	2 (4%)
Major bleeding	0 (0%)
Intracranial hemorrhage	0 (0%)
Allergic reactions	0 (0%)

Table 3 – Pharmacokinetic parameters in patients with acute myocardial infarction with ST-segment elevation

Parameter	Value (M ± SD)	Parameter	Value (M ± SD)
A, μg/L	5.56 ± 2.63	CL_1, L/min	0.33 ± 0.04
α, 1/min	0.32 ± 0.05	V_2, L	3.68 ± 0.74
B, μg/L	1.52 ± 0.14	CL_2, L/min	0.45 ± 0.07
β, 1/min	0.04 ± 0.00	AUC_{0-t}, μg/mL×min	42.9 ± 3.2
$t_{1/2\alpha}$, min	5.77 ± 0.72	$AUC_{0-\infty}$, μg/mL×min	68.02 ± 7.04
$t_{1/2\beta}$, min	32.08 ± 4.11	AUMC, μg/mL×min^2	3742.07 ± 831.14
C_0, μg/mL	7.1 ± 2.7	MRT, min	42.26 ± 5.57
V_1, L	6.62 ± 0.63	V_{ss}, L	10.3 ± 1.05

Table 4 – Baseline characteristics of patients

Characteristics	Indicator (*n* = 50)
Gender, male / female, *n* (%)	32 / 18 (64% / 36%)
Age, M ± SD, years	64.4 ± 9,6
Patients over 80 years old, *n* (%)	2 (4%)
Weight, Me (Q1; Q3), kg	80 (74; 90)
Body mass index, Me (Q1; Q3), kg/m^2	27.1 (24.7; 30.7)
Arterial hypertension, *n* (%)	48 (95%)
Atrial fibrillation, *n* (%)	20 (40%)
Smoking, *n* (%)	13 (26%)
Dyslipidemia, *n* (%)	10 (20%)
Stroke, *n* (%)	7 (13%)
Type II diabetes mellitus, *n* (%)	5 (10%)
Time from the onset of symptoms to TLT, M ± SD, h	2.9 ± 0.8
Median NIHSS before TLT, Me (Q1; Q3), points	11 (8; 14)
Median mRS before TLT, Me (Q1; Q3), points	4 (4; 5)
Focus localization, *n* (%): Right middle cerebral artery Left middle cerebral artery Vertebrobasilar basin	 22 (44%) 24 (48%) 4 (8%)

Note: TLT — thrombolytic therapy.

Table 5 – Assessment of the effectiveness and safety of non-immunogenic staphylokinase in patients with ischemic stroke

Criterion	Indicator (*n* = 50), *n* (%)
Number of patients with mRS 0-1 points at 90 days	25 (50%)
Median NIHSS after 24 hours, points	6 (3–11%)
Median NIHSS at 90 days, points	2 (1–5%)
Death from all causes at 90 days	5 (10%)
Symptomatic hemorrhagic transformation (ECASS-III)	1 (2%)
Major bleeding	0 (0%)
Myocardial infarction	0 (0%)
PE	0 (0%)
Allergic reactions	0 (0%)

Note: PE — pulmonary embolism.

Table 6 – Pharmacokinetic parameters in patients with ischemic stroke

Parameter	Value (M ± SD)	Parameter	Value (M ± SD)
A, μg/L	1.78 ± 0.29	CL_1, L/min	0.35 ± 0.06
α, 1/min	0.4 ± 0.1	V_2, L	3.62 ± 0.42
B, μg/L	1.02 ± 0.1	CL_2, L/min	0.51 ± 0.1
β, 1/min	0.03 ± 0.00	AUC_{0-t}, μg/mL×min	28.5 ± 3.6
$t_{1/2\alpha}$, min	5.11 ± 0.56	$AUC_{0-\infty}$, μg/mL×min	52.94 ± 4.11
$t_{1/2\beta}$, min	32.67 ± 2.12	AUMC, μg/mL×min^2	2424.95 ± 277.57
C_0, μg/mL	2.8 ± 0.3	MRT, min	38.71 ± 2.62
V_1, L	5.79 ± 0.66	V_{ss}, L	9.4 ± 0.8

Table 7 – Comparison of pharmacokinetic parameters of the main thrombolytic drugs

Parameter	Non-immunogenic staphylokinase, 10 mg	Non-immunogenic staphylokinase, 15 mg	Alteplase, 100 mg	Tenecteplase, 30–50 mg
$t_{1/2\alpha}$, min	5.11 ± 0.56	5.77 ± 0.72	3.5 ± 1.4	24 ± 5.5
$t_{1/2\beta}$, min	32.67 ± 2.12	32.08 ± 4.11	72 ± 68	129 ± 87
CL_1, L/min	0.35 ± 0.06	0.33 ± 0.04	0.57 ± 0.13	0.1 ± 0.05

Note: data are presented as M±SD.

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RESULTS

Study of the pharmacokinetics of non-immunogenic staphylokinase at a dose of 15 mg in patients with acute myocardial infarction with ST-segment elevation

The study included 50 patients with STEMI who received non-immunogenic staphylokinase once as a bolus at a dose of 15 mg. Demographic, anthropometric, anamnesis data, clinical characteristics, and time intervals are presented in Table 1.

The average age of patients was 58.9 ± 9.9 years. The proportion of patients with arterial hypertension was 37 patients (75%), previous myocardial infarction — 12%, lipid metabolism disorders — 86%. Inferior infarctions predominated in the study population (56%).

Assessment of the effectiveness and safety of TLT is presented in Table 2.

A decrease in the ST-segment after 90 min by 50% from the initial value was noted in 80% of patients. Restoration of coronary blood flow in the infarct-related artery according to TIMI 2 + TIMI 3 criteria was observed in 70% of patients. Death from all causes was 2%. No intracranial hemorrhages were registered with the use of non-immunogenic staphylokinase. No patients experienced major bleeding or hemorrhagic stroke. No allergic reactions were registered as a result of the study.

The averaged pharmacokinetic profile of non-immunogenic staphylokinase is presented in Figure 1.

Non-immunogenic staphylokinase is a short-lived molecule and is characterized by rapid elimination from the systemic circulation. Table 3 presents the pharmacokinetic parameters of non-immunogenic staphylokinase in patients with STEMI after a single bolus injection.

The initial concentration C_0 of non-immunogenic staphylokinase in blood plasma is 7.1 ± 2.7 μg/mL. The half-life $t_{1/2\alpha}$ of non-immunogenic staphylokinase, administered once as a bolus at a dose of 15 mg in patients with STEMI, is 5.77 ± 0.72 min, the terminal half-life $t_{1/2\beta}$ — 32.08 ± 4.11 min. The mean residence time of non-immunogenic staphylokinase in the systemic circulation (MRT) was 42.26 ± 5.57 min. Thus, non-immunogenic staphylokinase has a very short half-life and is rapidly metabolized to amino acids when passing through the liver.

The clearances of non-immunogenic staphylokinase were CL_1 = 0.33 ± 0.04 L/min and CL_2 = 0.45 ± 0.07 L/min. High clearance rates indicate rapid elimination of the staphylokinase molecule from the systemic circulation. The area under the pharmacokinetic curve within the duration of observation AUC_{0-t} was 42.9 ± 3.2 μg/mL×min, the area under the pharmacokinetic curve from 0 to infinity $AUC_{0-\infty}$ was 68.02 ± 7.04 μg/mL×min. The area under the curve from 0 to infinity with extrapolation of the final phase (AUMC) was 3742.07 ± 831.14 μg/mL×min^2.

The apparent volume of distribution of the drug at steady state (V_{SS}) was 10.3 ± 1.05 L. The magnitude of the apparent volume of distribution is not equivalent to the physiological volume, but reflects the distribution of the drug and the degree of its binding in the body. V_{SS} of non-immunogenic staphylokinase showed an excess of the value over the real volume of circulating blood, which indicates the elimination of the drug from the systemic circulation and probable penetration into the thickness of the thrombus, which is consistent with the available data on the pharmacodynamics of the staphylokinase molecule.

Study of the pharmacokinetics of non-immunogenic staphylokinase at a dose of 10 mg in patients with ischemic stroke

The study included 50 patients with ischemic stroke who received non-immunogenic staphylokinase once as a bolus at a dose of 10 mg. Demographic, anthropometric, anamnesis data, clinical characteristics, and time intervals are presented in Table 4.

The average age of patients was 64.4 ± 9.6 years. The proportion of patients with arterial hypertension was 95%, previous stroke — 13%, lipid metabolism disorders — 20%. The median NIHSS at admission was 11 (8–14) points. The average time from the onset of symptoms to thrombolysis was 2.9 ± 0.8 h

Assessment of the effectiveness and safety of TLT is presented in Table 5.

The number of patients with good functional recovery (0–1 points on the modified Rankin Scale) on day 90 was 50%. 24 hours after thrombolysis, a decrease in the median NIHSS from 11 to 6 points was noted, by the 90 day — to 2 points. Mortality from all causes on the 90th day was 10%. Symptomatic hemorrhagic transformation according to ECASS-III criteria was registered in 1 patient (2%). No major bleeding or allergic reactions were registered.

The averaged pharmacokinetic profile of the medicine in patients with ischemic stroke is presented in Figure 2.

It has been shown that the kinetic profile of non-immunogenic staphylokinase in patients with ischemic stroke is similar to that in patients with STEMI: the drug is characterized by a short half-life and rapid elimination from the bloodstream. Based on the concentration values of non-immunogenic staphylokinase in the blood, pharmacokinetic parameters were calculated when using the drug at a dose of 10 mg (Table 6).

The initial concentration C_0 of non-immunogenic staphylokinase in patients with ischemic stroke in blood plasma was 2.8 ± 0.3 μg/mL. The half-life $t_{1/2\alpha}$ is 5.11 ± 0.56 min, the terminal half-life $t_{1/2\beta}$ — 32.67 ± 2.12 min. The mean residence time of the drug in the systemic circulation (MRT) was 38.71 ± 2.62 min. These values are slightly lower than the indicators obtained in patients with STEMI due to the fact that the drug was administered at a lower dose (10 mg vs 15 mg). The clearances CL_1 and CL_2 were 0.35 ± 0.06 L/min and 0.51 ± 0.1 L/min, respectively, and are generally similar to the clearance values of non-immunogenic staphylokinase in patients with STEMI. The area under the pharmacokinetic curve within the duration of drug observation AUC_{0-t} was 28.5 ± 3.6 μg/mL×min, the area under the pharmacokinetic curve from 0 to infinity $AUC_{0-\infty}$ — 52.94 ± 4.11 μg/mL×min. The area under the curve from 0 to infinity with extrapolation of the final phase (AUMC) was 2424.95 ± 277.57 μg/mL×min^2. The apparent volume of distribution of the drug at steady state in ischemic stroke is slightly lower than in patients with STEMI (9.41 ± 0.8 L vs 10.3 ± 1.05 L), which is probably due to the smaller volume of thrombotic masses in the occlusion of cerebral arteries.

DISCUSSION

This article presents the results of a study of the pharmacokinetic parameters of non-immunogenic staphylokinase after its single bolus administration in patients with STEMI and ischemic stroke. It was established that both at a dose of 15 mg and at a dose of 10 mg, non-immunogenic staphylokinase is characterized by a short half-life (5.11 min and 5.77 min, respectively), the terminal half-life was 32 min in both dosing options, clearance — 0.35 L/min and 0.33 L/min, respectively. It is important to note that these results correspond to the results of a study of the pharmacokinetics of the staphylokinase molecule used at a dose of 10 mg in patients with STEMI [24]: it was shown that its half-life was 6.3 ± 0.6 min; the terminal half-life was 37 ± 15 min. The clearance of the staphylokinase molecule was 0.27 ± 0.1 L/min.

Table 7 shows the main pharmacokinetic parameters of the most commonly used thrombolytic drugs [25]. The half-life of non-immunogenic staphylokinase is the closest to that of the tissue plasminogen activato — alteplase. It is important to note that alteplase is used as a bolus-infusion for 1–2 hours depending on the indication, and the dose is selected individually from the patient's body weight, which greatly complicates its use in emergency medical care and may be the cause of dosing errors. The pharmacodynamic properties of non-immunogenic staphylokinase associated with its interaction with plasmin in the thrombus and subsequent recirculation of released drug molecules allow it to be used in lower doses regardless of the patient's body weight, despite the short half-life. Tenecteplase is a modified alteplase molecule created for single bolus administration. The half-life of tenecteplase is 24 ± 5.5 min, which is significantly higher than that of non-immunogenic staphylokinase and alteplase, however, tenecteplase, like alteplase, requires dose selection depending on the patient's body weight.

The pharmacodynamic and pharmacokinetic properties of the non-immunogenic staphylokinase molecule are reflected in clinical practice. Thus, according to the registry of patients with STEMI "REGION-IM", conducted under the auspices of the National Medical Research Center of Cardiology named after Academician E.I. Chazov, 36% of patients with STEMI receive TLT using non-immunogenic staphylokinase, and at the prehospital stage this figure reaches 42%. The frequency of use of non-immunogenic staphylokinase in primary vascular departments reaches 51% [26]. The pharmacokinetic features of non-immunogenic staphylokinase determine the convenience of its use, especially in emergency medical care. Timely TLT for patients with STEMI using drugs with rapid bolus administration allows accelerating reperfusion, preserving the myocardium, and reducing the burden of complications of cardiovascular diseases, since it is known that every 5% increase in the size of the myocardial infarction zone

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contributes to an increase in one-year mortality from all causes or hospitalization for heart failure within a year by 20% [27]. Monitoring the use of non-immunogenic staphylokinase in real clinical practice includes more than 50 thousand patients, in whom high safety and effectiveness of the treatment are shown [28]. Non-immunogenic staphylokinase is included in the current list of Vital and Essential Drugs, Russian and Eurasian clinical guidelines and standards for the treatment of patients with STEMI.

In 2024, non-immunogenic staphylokinase was included in the clinical guidelines for the treatment of ischemic stroke in the first 4.5 hours from the onset of the disease. A rapid (10 sec) single bolus of non-immunogenic staphylokinase at a single dose of 10 mg in patients with ischemic stroke with any body weight, including those weighing more than 100 kg, has advantages over a one-hour administration of alteplase at a dose of 0.9 mg/kg (maximum 90 mg) in the form of faster reperfusion and a greater number of good functional outcomes.

According to the FORPE study, non-immunogenic staphylokinase, administered as a single bolus at a dose of 15 mg, is effective in the treatment of massive pulmonary embolism (PE) [29]. Currently, a double-blind placebo-controlled clinical trial of non-immunogenic staphylokinase is being conducted in patients with intermediate-high risk PE (permission of the Russian Ministry of Health No. 106 dated March 21, 2024; clinicaltrials.gov No.NCT06362746) [30]. A clinical trial of non-immunogenic staphylokinase is being conducted with its intra-arterial intratrombal administration in patients with thrombosis of the arteries of the lower extremities in comparison with surgical methods of treatment FORAT (permission of the Russian Ministry of Health No. 184 dated March 18.03, 2022; clinicaltrials.gov No. NCT05372718) [31]. It is expected that the pharmacokinetic features of non-immunogenic staphylokinase will contribute to the expansion of indications for safe TLT.

Study Limitations

The pharmacokinetics of non-immunogenic staphylokinase have not been studied with bolus-infusion dosing regimen (10 mg bolus and 5 mg infusion) due to the low prevalence of this regimen. According to observational studies, 96% of patients receive the drug as a single bolus at a dose of 15 mg [28].

CONCLUSION

This article presents the results of a study of the pharmacokinetic parameters of non-immunogenic staphylokinase after a single bolus administration in patients with STEMI and ischemic stroke. The features of the pharmacokinetics and pharmacodynamics of the non-immunogenic staphylokinase molecule are that with a short half-life, high clearance and low dose, the drug has a pronounced fibrinolytic effect, not inferior in effectiveness to other thrombolytic drugs administered bolus and bolus-infusion in significantly higher doses. The data obtained in the course of these studies explain the high efficacy and safety of TLT using non-immunogenic staphylokinase.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Sergei V. Ivanov — writing—original draft; Igor P. Beletsky — research design, administration; Marina V. Zakharova — conducting research, statistical data processing; Eduard A. Ponomarev — conducting research; Zhanna Yu. Chefranova — investigation; Sergey L. Konstantinov — investigation; Galina I. Stryabkova — investigation; Yurij A. Lykov — investigation; Ulukpan A. Yelemanov — investigation; Svetlana E. Chuprina — investigation; S.S. Markin — research design, writing-review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication)

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