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Research Article Rus

2-phenyl-1-(3-pyrrolidin-1-il-propyl)-1 H-indole hydrochloride (SS-68): Antiarrhythmic and cardioprotective activity and its molecular mechanisms of action (Part I)

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Abstract

Introduction. The problem of heart rhythm disturbances is one of the most urgent topics of modern cardiology. According to the currently available concepts, 1,2- and 1,3-disubstituted aminoindole derivatives, which compound 2-phenyl-1-(3-pyrrolidin-1-il-propyl)-1H-indole hydrochloride (SS-68) belongs to, are a promising chemical group in terms of their cardio-pharmacological activity.

Materials and methods. To study the anti-arrhythmic activity of SS-68 compound, the following models were used: 1) Models of cardiogenic arrhythmia: aconitine-inducedic, calcium chloride-induced, barium chloride-induced, cesium chloride-induced, adrenaline model of arrhythmia, strophanthine-induced arrhythmias, as well as arrhythmias caused by electrostimulation and acute myocardial ischemia; 2) neurogenic arrhythmias: arrhythmias caused by administration of aconitine, strophanthine K, cesium chloride into the IV ventricle of the brain and also by applying carbachol on the somatosensory cortex. To assess the antianginal activity of SS-68 in various models, the effect of this drug and comparators on the intact and ischemic myocardium was studied.

Results. It was found that with cardiogenic arrhythmias, SS-68 compound exhibits a pronounced antiarrhythmic effect and brings to normal the electrophysiological pattern of the heart, in most cases exceeding the analogous effect of reference drugs (amiodarone, lidocaine, aymaline, ethacizine, etmozine, quinidine anaprilin). In neurogenic arrhythmias, SS-68 also had a stopping effect, and, in addition, reduced the epileptiform activity of the brain in the model with the application of carbachol on the somatosensory cortex. In the study of antianginal and coronary vasolidating activities, SS-68 demonstrated pronounced thrombolytic and anti-ischemic activities, manifested in an increase in the coronary blood flow, a positive effect on ST-segment depression, and a decrease in the area of necrosis in experimental myocardial infarction.

Discussion. The antiarrhythmic and antianginal activities of SS-68 compound create the prerequisites for further study of the pharmacological properties of this molecule. In addition, it seems appropriate to continue studying the pharmacodynamics, pharmacokinetics and molecular mechanisms of SS-68 action.

Conclusions. SS-68 compound is a promising pharmacological agent with a high activity towards various electrophysiological disorders in the heart, and, in addition, it has significant antiischemic and coronary vasolidating properties.

Keywords

arrhythmias, antiarrhythmics, infarction, angina pectoris, SS-68.

Introduction

According to the World Health Organization, every year more than 17 million people die of cardiovascular diseases and related complications, including heart rhythm disturbances (HRD), especially atrial fibrillation (AF) (Golitsyn 2008, Karpov and Sorokin 2012, Opii and Gersh 2010, Roger et al. 2011).

The prevalence of AF as the most common cause of disability and a decline in the quality of life in Russia is 3.2 per 1000 people (2.8 and 3.6 in men and women, respectively) (Serdechnaya et al. 2007). AF leads to a decrease in exercise tolerance, development of heart failure, and a 5 to 7-fold increase in the risk of occurrence (in 4.2-7.2% of cases) of thromboembolic complications, in particular ischemic stroke (Bunin and Mikishanskaya 2018). Mortality of patients with AF range from 2.9 to 4.2% (Serdechnaya et al. 2009, Revishvili et al. 2015, Belousov et al. 2017, Serdechnaya et al. 2007, Gladstone et al. 2009, Naccarelli et al. 2009). Most of the antifibrillatory drugs used in cardiac practice have serious deficiencies, the main of which are narrow therapeutic windows (TW) and a number of cardiac and extracardiac side effects (Kryzhanovsky and Vititnova 2008, Galenko-Yaroshevsky et al. 2012a, 2012b, 2012f, DiMarco et al. 2010, Crea et al. 2011).

Solving the problems of treating patients with AF can be significantly promoted by new antifibrillatory drugs, more effective and less toxic than the existing ones (Galenko-Yaroshevsky and Gatsura 2009, 2011, Galenko-Yaroshevsky et al. 2012a, Nesterenko et al. 2014). What is important is that the newly created antiarrhythmic drugs, along with their high activity, also have positive pleiotropic (multiple) properties (Galenko-Yaroshevsky and Gatsura 2009, Grigorieva 2010, Belenkov et al. 2011, Titenkov 2012, Zannad et al. 2011). The latter is due to the fact that multicomponent therapy is very important both for the treatment of patients with AF and for the prevention of its complications (Revishvili et al. 2015, Zannad et al. 2011).

According to the published data, indole derivatives can exhibit antiarrhythmic, antiischemic (antianginal), antihypertensive, antiaggregant, anti-sclerotic, anti-inflammatory, analgesic and other properties (Amelin et al. 2010, Mashkovsky 2010, DiMarco et al. 2010, Crea et al. 2011).

Based on the foregoing, it seems reasonable to study the pharmacological activity of the new 1,2- and 1,3-disubstituted amino derivatives of indole, in particular 2-phenyl-1-(3-pyrrolidin-1-il-propyl)-1H-indole hydrochloride (SS-68 compound).

Materials and methods

The experiments were carried out in accordance with the requirements of GOST ISO/IEC 1704-2009, GOST R ISO 5725-2002 and *The Rules of laboratory practice* approved by Order № 708n of the Ministry of Health and Social Development of the Russian Federation on August 23, 2010, in compliance with *The European Convention for the Protection of Vertebrates Used for Experiments or Other Scientific Purposes* (Directive 2010/63/EU). The experiments were conducted in accordance with *The Guidelines for Pre-clinical Study of Medicinal Products* (2012).

The aconitine-induced arrhythmia model was reproduced on nonlinear conscious and anesthetized (ethaminal-sodium 40-50 mg/kg intraperitoneally) male rats (Galenko-Yaroshevsky et al. 2012c).

Calcium chloride-induced arrhythmia model was used in experiments on conscious nonlinear rats (Galenko-Yaroshevsky et al. 2012c).

Barium chloride-induced arrhythmia model was used on conscious rabbits (Galenko-Yaroshevsky et al. 2012d).

Cesium chloride-induced arrhythmia model was studied in experiments on anesthetized (urethane 1.0-1.3 g/kg intraperitoneally) nonlinear male rats (Galenko-Yaroshevsky et al. 2012a, 2012d).

Adrenaline model of arrhythmia was used on anesthetized rats by rapid intravenous injection of an adrenaline solution at a dose of 0.3 mg/kg (Mironov 2012).

Strophanthine-induced arrhythmia model was used on anesthetized cats (etaminal-sodium 50 mg/kg intraperitoneally) (Mironov 2012).

Ventricular HRDs (in the late stage of myocardial infarction (MI)) were induced in experiments in anesthetized (ethaminal-sodium 40 mg/kg intrapleurally) dogs (Galenko-Yaroshevsky et al. 2012c).

The antifibrillatory activity of substances was studied in experiments on anesthetized cats (etaminal-sodium 40 mg/kg intraperitoneally) by determining the threshold of ventricular fibrillation (VF) of the heart (Hageman et al. 1986, Mironov 2012). VF was caused by the electrostimulator designed by (Storozhuk and Naumov 1981), which allows applying rectangular electrical pulses starting from 2 mA, duration from 5 to 200 ms in the sensitive period of the ECG, recorded in the 2nd standard lead. Defibrillation was performed with an ID-66 defibrillator at a voltage of 2.5 to 3.5 kV. The current discharge was applied onto the chest of the animal. The experiments were performed on animals with intact and infarcted myocardium, while MI was induced by occlusion of the left anterior descending artery (LAD) at the border of its upper and middle thirds.

Early post-occlusion (EPOA) and reperfusion arrhythmias (ERA) were caused in anesthetized (sodium-ethanol 40 mg/kg intraperitoneally) cats according to the methods described in (Gendenshtein et al. 1990).

The influence of the substances on the effective refractory period of the atria was studied in experiments on isolated atrial appendages of guinea pigs of both sexes according to the method described in (Senova 1963).

The influence on HRD induced by mechanical destruction of the sinus node and subsequent electrostimulation of the atria in dogs. The experiments were performed in anesthetized (pentobarbital-sodium 40 mg/kg intravenously or 50 mg/kg intrapleurally) dogs of both sexes according to the method described in (PA Galenko-Yaroshevsky et al. 2012d).

The influence on HRD induced by paired atrial stimulation against vagal cardiac arrest initiated by tonic stimulation of the vagal nerve (VN). The experiments were performed in anesthetized (1% mixture of α-chloralose and ethaminal-sodium 75 and 15 mg/kg, respectively) cats using the method of (Sheikh-Zade et al. 1985).

The influence on the dynamics of the excitation focus in the sino-atrial node (SAN) during VN stimulation was studied in experiments in anesthetized (urethane 1.2 g/kg intraperitoneally) cats according to the method described in (Somov and Pokrovsky 2014).

The influence on the pool dynamics on pools of the initial excitation source in SAN in kittens with idiopathic sick sinus syndrome was studied in anesthetized (urethane 1.2 g/kg intraperitoneally) kittens according to the method described in (Somov and Pokrovsky 2014).

A study of the influence of the test substances on arrhythmias induced by administering aconitin, strophanthine K and cesium chloride into the IV ventricle of the brain was performed in anesthetized (40 mg/kg of α-chloralose and 30 mg/kg of ethaminal-sodium intraperitoneally) cats (Galenko-Yaroshevsky et al. 2012c).

The influence on the bioelectrical activity of somatosensory cortex (SSC) and HRD induced by microapplication of carbachol (CCh) on cortical structures of the brain was investigated in experiments in white nonlinear rats of both sexes according to the method described in (Sukhov et al. 2011).

The influence on the coronary artery flow velocity (CAFV) was studied in anesthetized (ethaminal-sodium 40-50 mg/kg intraperitoneally) cats of both sexes by the method by (Moravitz and Zahn 1912) in the modification of Kaverina (1958). At the same time, blood pressure in the carotid artery and heart rate were recorded. Myocardial oxygen demand (MOD) was calculated by the rate pressure product method (RPP), which is a BP × heart rate × 10^{-3}.

The influence of intracoronary injection of SS-68 compound on the phasic coronary blood flow (PCBF) was studied in experiments in dogs; systemic arterial blood pressure, reactive hyperemia (RH) lasting 20 sec (Khomazyuk 1985), left ventricular pressure (LVP), the rate of its changes (dP/dt+and dP/dt-) and heart rate (HR) were recorded (Sheikh-Zade 1985, Konstantinov et al. 1986, Orlov et al. 1987).

The influence on myocardial contractility and the phase structure of the cardiac cycle (PSCC) was studied in experiments in anesthetized (ethaminal-sodium 40 mg/kg intraperitoneally) cats according to (Sheikh-Zade 1985). The durations of the cardiac cycle (DCC), of the phases of asynchronous (DPAC) and isometric contraction (DPIC), of the periods of tension DPT) and ejection (DPE), of the systole (DS), of the diastole (DD) and of P-Q and Q-T ECG intervals were determined, as well as LVP, the maximum discharge rate/temperature drop in the left ventricle (dP/dt+). Evaluation of the phase structure of the cardiac cycle and myocardial contractility was performed according to the ADM.

The influence on the main indicators of heart activity and hemodynamics was investigated in experiments on rats and cats. After fixing the anesthetized (urethane 1.3 g/kg intraperitoneally) white non-linear male rats on the operating table, the left femoral artery was catheterized to measure systemic blood pressure. Through the left common carotid artery, an ultrasonic sensor was inserted into the cavity of the left ventricle of the heart. The right femoral vein was catheterized for introducing the test compound. Simultaneously, ECG was recorded in the II standard lead. Based on the analysis of the recorded values, the following indicators of hemodynamics and heart activity were calculated according to the methods described in (Galenko-Yaroshevsky and Gatsura 2005): mean systolic blood pressure (SBP); heart rate; stroke volume of blood (SV); minute blood volume (MV); total peripheral resistance (TPR); and myocardial contractility (dP/dt). When studying cardiac activity and general hemodynamics in experiments in narcotized (ethaminal-sodium 40 mg/kg intraperitoneally) cats, the thermodilution method was used. At the same time, MV and SV, cardiac output (Q_c), cardiac (CI) and systolic pressure indices (SPI), left ventricle work index (LVWI) and left ventricle stroke index (LVSI), TPR, BP and heart rate were selected as indicators of cardiohemodynamics.

The influence on CAFV, mean BP, MV and SV, contractility (dP/dt+and dP/dt-) of the myocardium, heart rate were examined under conditions of ischemic (by occlusion of the anterior interventricular branch of the left coronary artery – LAD on the border of the middle and lower third) of the myocardium in anesthetized (ethaminal-sodium 50 mg/kg intrapleurally) dogs, using an RM-600 recorder by Nihon Kohden.

The collateral circulation (CC) was examined by means of recording the volume velocity of the retrograde blood flow (VVRF) ligated in the distal part of the LAD in anesthetized dogs (ethaminal-sodium 50 mg/kg intraperitoneally) (Gatsura and Bandurina 1964). The ability of the substance to cause a redistribution of blood flow to the area of the ischemic site was estimated by the blood redistribution rate (BRR), which is the ratio of VVRF to BP, expressed as a percentage (Saratikov et al. 1980). Along with the study of collateral circulation, changes in heart rate and MOD were studied. The latter indicator was calculated by the DP method (Galenko-Yaroshevsky et al. 2012c). Based on the DP, the myocardial CC was determined, which is the ratio of VVRF to DP, expressed as a percentage.

The influence on coronary circulation under conditions of myocardial ischemia induced by pituitrin was studied in experiments in anesthetized cats (ethaminal-sodium 40 mg/kg intraperitoneally). Spasm of the coronary vessels was caused by intravenous injection of pituitrin (5 units/kg) (Mironov 2012).

The cardioprotective effect was studied in experiments in anesthetized (chloral hydrate 300 mg/kg) chinchilla breed rabbits. MI in animals on controlled respiration was caused by ligating LAD at the level of the lower edge of the left atrial appendage. Thirty minutes before the ligation of the coronary artery, SS-68 at a dose of 2 mg/kg was injected into a rabbit's marginal ear vein. Mildronate (Grindeks, Latvia) at a dose of 80 mg/kg was also administered intravenously 30 minutes beforehands. Similarly, 30 minutes before ischemia, a 5-minute episode of ischemic preconditioning was performed. Thirty minutes after coronary occlusion, the ligature was removed and myocardial reperfusion was performed for 90 minutes, after which blood was drawn from the right ventricle into a disposable vacuum tube with an anticoagulant to determine a specific marker of the cardiac muscle, troponin I. The level of troponin was determined on an immunorefluorescence device Triage MeterPro (Biosite, USA), using the Cardiac Panel test system.

The evaluation of the area of necrotic myocardium was performed after the 1.5-hour reperfusion. Transverse sections of the myocardium were cut at each 0.8-cm interval, starting from the level of 0.8 cm below the site of the ligature. Sections of the myocardium were placed in a container with phosphate buffer (pH=7.4) and 1 mg/ml of triphenyltetrazolium chloride for forming red formazan. The areas of the intact and necrotic left ventricular myocardium were calculated on each of the 4 slices by means of pixel analysis via Adobe Photoshop 9.0.

The functional state of the ischemic focus of the myocardium was studied in experiments in anesthetized cats (ethaminal-sodium 40 mg/kg intraperitoneally), with ischemia modeled by occlusion (5 min) LAD in the middle third (Goldsteine 1984).

The antianginal activity of the substances was evaluated by the depression of the total amount of the ST segment of the epicardial electrogram recorded from 6 points on the heart surface. The significant results were those in which the ST segment depression was higher than 10% (Galenko-Yaroshevsky et al. 2012e).

Experimental MI was modeled in the anesthetized cats (ethaminal-sodium 40 mg/kg intraperitoneally) by occlusion of left anterior descending artery (LAD) at the border of the its upper and middle thirds, the size of the necrotic zone (NZ) was studied according to the method described in (Gatsura 1986).

Results

Depending on the selected models of arrhythmia, SS-68 compound and reference drugs for antiarrhythmic activity can be represented in the following lines:

In aconitine-induced arrhythmia in conscious rats – amiodarone>SS-68 compound = lidocaine (Fig.1);

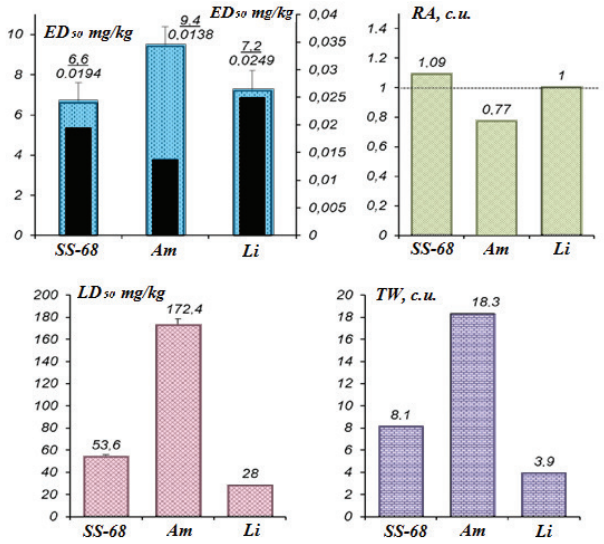

Figure 1. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) SS-68, amiodarone (Am) and lidocaine (Li) in the prevention of aconitine-induced arrhythmia in experiments in conscious rats. Note: here and henceforward ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In aconitine-induced arrhythmia in anesthetized rats – amiodarone>SS-68 compound = lidocaine (Fig. 2);

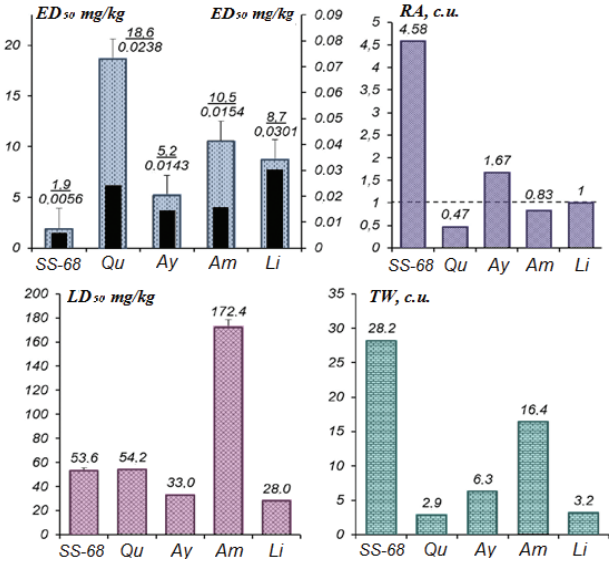

Figure 2. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, quinidine (Qu), Aymalin (Ay), amiodarone (Am), and lidocaine (Li) used to arrest aconitine-induced arrhythmia in experiments in anesthetized rats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In calcium chloride-induced arrhythmia (rats) – verapamil>SS-68 compound>amiodarone (Fig. 3);

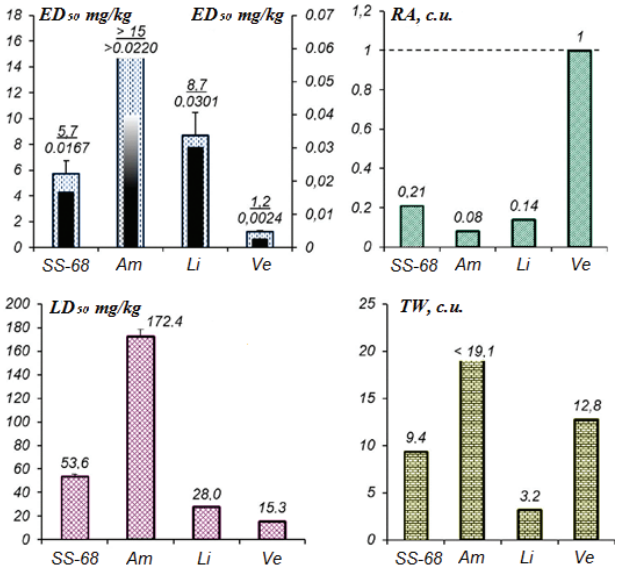

Figure 3. Comparative activity [by ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, amiodarone (Am), lidocaine (Li), and verapamil (Ve) used to prevent calcium chloride-induced arrhythmia in experiments in conscious rats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

The conducted experiments showed that SS-68 compound can not prevent heart rhythm disturbances caused by calcium chloride, but only reduces the mortality of animals. Proceeding from this property of SS-68 compound, the antiarrhythmic action of this compound and the reference drugs were evaluated by the survival rate of the animals.

It was established that SS-68 compound, when ED_{50} is expressed in mg/kg, by its antiarrhythmic activity exceeds lidocaine and amiodarone 1.5 or over 2.6 times (at a dose of 15 mg/kg, antiarrhythmic effect was observed in 2 animals out of 10, which did not allow determining ED_{50}), but was 4.8 times worse than verapamil. When ED_{50} is expressed in mM/kg, SS-68 compound in this respect exceeds lidocaine and amiodarone 1.8 and over 1.3 times, and is 7.0 times more than verapamil. By TW, SS-68 compound exceeds lidocaine 2.9 times, but is 1.4 and 2.0 times worse than verapamil and amiodarone (conventionally) (Fig. 3);

In barium chloride-induced arrhythmia (rabbits) – SS-68 compound>quinidine> amiodarone (Fig. 4);

It was established that SS-68 compound – with ED_{50} expressed in mg/kg and mM/kg – shows a very pronounced antiarrhythmic effect. So, by this effect, this substance exceeds amiodarone and quinidine 50.0 and 84.4, 22.0 and 32.3 times, respectively. By TW, SS-68 compound exceeds amiodarone and quinidine 1.6 and 8.4 times (Fig. 4);

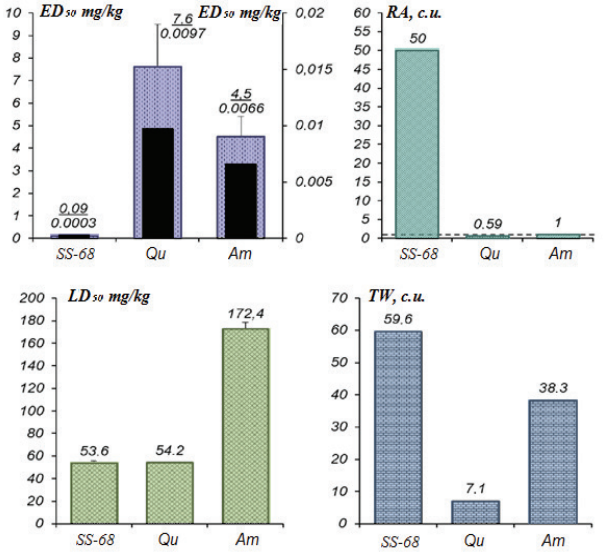

Figure 4. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, quinidine (Qu) and amiodarone (Am) used to arrest barium chloride-induced arrhythmia in experiments in conscious rabbits. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In cesium chloride-induced arrhythmia (prophylactic action) in rats – SS-68 compound> amiodarone (Fig. 5);

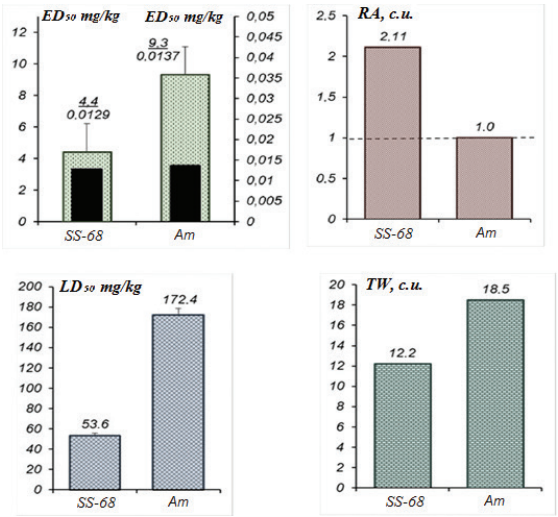

Figure 5. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68 and amiodarone (Am) used to prevent chloride cesium arrhythmia in experiments in anesthetized rats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In cesium chloride-induced arrhythmia (arrest) in rats –. SS-68 compound>amiodarone (Fig. 6)

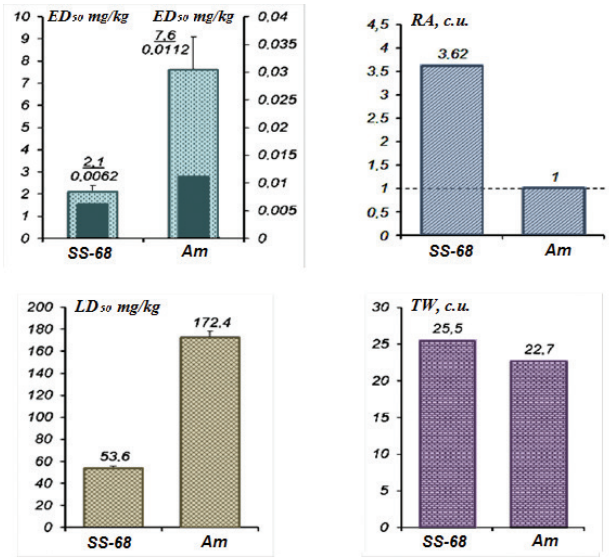

Figure 6. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68 and amiodarone (Am) used to treat cesium chloride-induced arrhythmia in experiments in anesthetized rats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In adrenaline-induced arrhythmia (rats) – anaprilin>atenolol>SS-68 compound> amiodarone (Fig. 7);

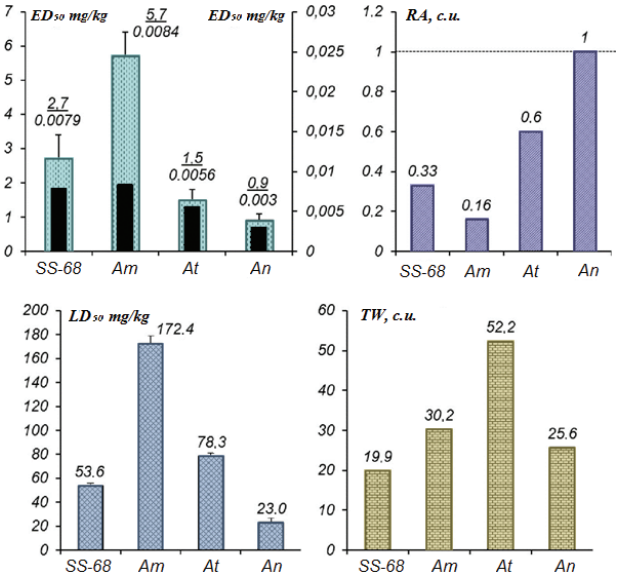

Figure 7. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, amiodarone (Am), atenolol (At), and anaprilin (An) used to prevent adrenal-induced arrhythmia in experiments in anesthetized rats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

In strophanthine-induced arrhythmia (cat) – verapamil>aymalin>SS-68 compound> quinidine>lidocaine (Fig. 8);

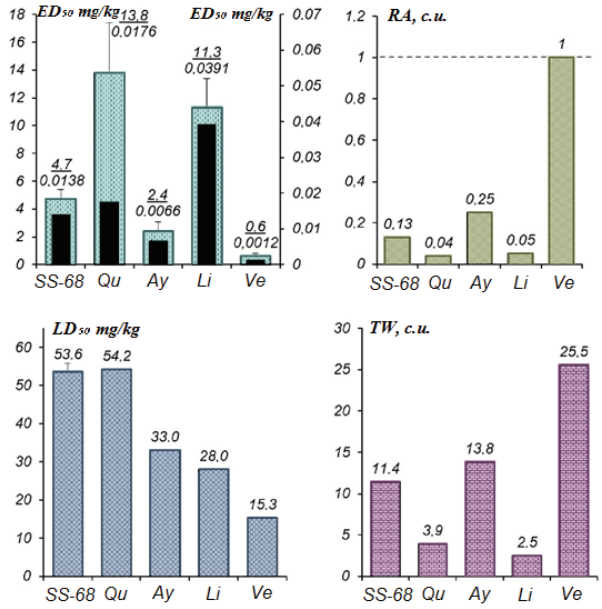

Figure 8. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, quinidine (Qu), aymalin (Ay), lidocaine (Li), and verapamil (Ve) used to arrest strophanthine-induced arrhythmia in experiments in anesthetized cats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

SS-68 compound demonstrated the most significant activity in conditions of barium chloride-induced arrhythmia, which is specific for class III antiarrhythmics (blockers of K^+-channels), in this respect exceeding amiodarone and quinidine 50 and 85 times, respectively (Fig. 4);

Antiarrhythmic activity in ventricular arrhythmias

The influence on heart rhythm disturbances caused by a two-stage coronary artery ligation in anesthetized dogs.

The conducted studies showed that for SS-68 compound the threshold anti-arrhythmic dose (TAD), which terminates ventricular tachycardia and extrasystole under the accepted experimental conditions, is 2.8±0.4 mg/kg, whereas for lidocaine it is 7.2±0.9 mg/kg, i.e., TAD of the former is 2.6 times less ($p<0.01$) than that of the latter (Fig. 9). It is important to note that for SS-68 compound the highest TAD is 4 mg/kg, and for lidocaine – 8 mg/kg, respectively, which makes up 7.5 and 28.6% of their LD_{50} (with intravenous administration to rats).

SS-68 compound and lidocaine by their ability to maximally reduce the number of ectopic ventricular contractions (EVC) (4.0±1.9% vs. 1.8±0.9%, $p> 0.05$),

the maximal antiarrhythmic effect (MAE) (2.6±0.2 min vs. 2.0±0.4 min, p> 0.05) and the decrease time of antiarrhythmic effect by 50% – DAE_{50} (10.0±2.1 min vs. 9.0±2.1 min, p> 0.05) were almost comparable (Fig. 9). Under the influence of SS-68 compound (122.6±4.4 bpm vs. 139.2±6.7 at the end, by 88.4%, p>0.05) and lidocaine (135.0±10.5 bpm vs. 148.8± 10.3 bpm at the end, by 90.7%; p>0.05), the heart rate tends to decrease (Fig. 9). When using SS-68 compound (4 mg kg, 1% solution) and lidocaine (8 mg/kg, 1% solution) in their maximum TADs, it was found out that 1, 3, 5 and 10 minutes after its intravenous administration, SS-68 compound exerted the most significant antiarrhythmic effect: the amount of EVC is 1.8±0.9, 1.2±0.6, 0.6±0.2 and 1.2±0.6%, respectively, against 74.2±7.7% at the end (in all cases p<0.001). In the subsequent time intervals – at the 15th (10.2±3.9%, p<0.001), 20th (15.6±3.5, p<0.001), 30th (25.3±4.3%, p<0.01), 40th (36.4±5.2%, p<0.001) and the 50th minutes (52.8±4.9%, p<0.05) – antiarrhythmic effect of SS-68 compound gradually decreased, remaining statistically reliable; at the 60th minute, the number of EVC is comparable to such number of the background. The heart rate decreased somewhat (a trend within 50-60 min) (Fig. 9).

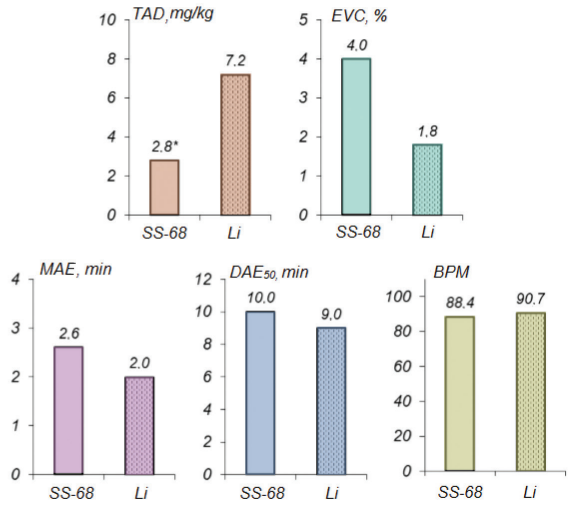

Figure 9. Comparative activity (according to TAD) of SS-68 and lidocaine (Li) in ventricular arrhythmias caused by a two-stage coronary artery litigation in dogs. Note: TAD – threshold antiarrhythmic dose, EVC – ectopic ventricular contractions, MAE – maximum antiarrhythmic effect, DAE_{50} – decrease in antiarrhythmic effect by 50%, BPM – beats per minute (heart rate). * – the differences are statistically significant at p<0.01 compared with lidocaine.

Thus, SS-68 compound in conditions of ventricular arrhythmia caused by a two-stage coronary artery litigation in dogs has antiarrhythmic effect, considerably exceeding lidocaine in this respect. Both SS-68 compound and lidocaine tend to reduce the heart rate.

Antifibrillatory activity in conditions of intact and infarcted myocardium in cats

As a result of the experiments, it was established that SS-68 compound at a dose of 5 mg/kg (1% solution, intravenously) in the conditions of the intact myocardium, by the ability to increase the ventricular fibrillation threshold (VFT), exceeds amiodarone at a dose of 10 mg/kg (1% solution, intravenously) 1.4 times, however, it is 1.2 times worse to it by the duration of action (Fig. 10).

With MI caused by occlusion of LAD, SS-68, as in the previous series of experiments, is 1.4 times more effective in its antifibrillatory activity than amiodarone. As for the duration of action, SS-68 is somewhat (1.2 times) superior to amiodarone, but these differences were statistically unreliable (Fig. 10). Thus, SS-68 compound in experiments with cats in conditions of the intact myocardium by its antifibrillatory activity is superior to amiodarone, and is inferior to it by the duration of action.

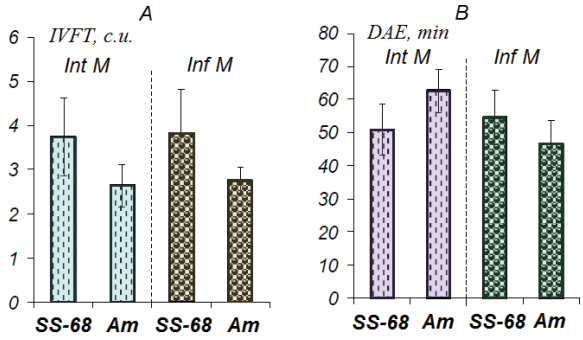

Figure 10. Comparative antifibrillatory activity (A) and duration of action (B) of SS-68 (5 mg/kg) and amiodarone (Am; 10 mg/kg) under conditions of intact (IntM) and infarcted myocardium (InfM) in cats. Note: IVFT – increased ventricular fibrillation threshold, DAE – duration of antifibrillatory effect.

The effect on early post-occlusive and reperfusion arrhythmias in cats

It was found that in the control group of animals, early occlusive arrhythmias (EOA) did not occur in 58.3% of cases, and early reperfusion arrhythmias (ERA) occurred in 100% of cats, while in 75.0% of cases ventricular fibrillation (VF) occurs (Fig.11).

SS-68 compound at a dose of 2 mg/kg did not have a preventive effect with respect to EOA, ERA and VF. Use of SS-68 at a dose of 5 mg/kg prevented EOA in 50.0% of cases; ERA and VF did not occur in 100.0 and 83.3% of animals, respectively (Fig. 11).

Thus, SS-68 at a dose of 2 mg/kg has no significant effect on EOA and ERA, including VF, and at a dose of 5 mg/kg exhibits significant antiarrhythmic and antifibrillatory effects, exceeding lidocaine (7 mg/kg) in this respect and is almost comparable to amiodarone (10 mg/kg).

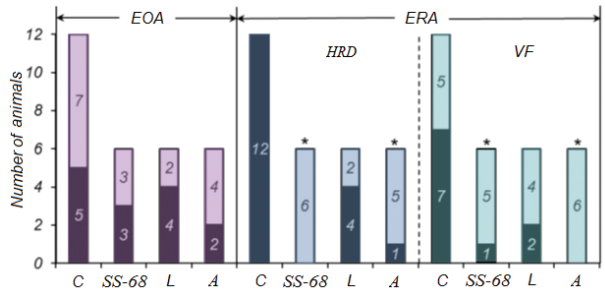

Figure 11. Comparative activity of SS-68 (5 mg/kg), lidocaine (L; 7 mg/kg) and amiodarone (A; 10 mg/kg) in early occlusive (EOA) and reperfusion arrhythmias (ERA) in cats. Note: C – control, HRD – heart rhythm disturbance, VF – ventricular fibrillation of the heart. The figures in the light part of the bar charts are the number of animals without either arrhythmia or VF, in the dark part – the number of animals with arrhythmia and VF. * – the differences are statistically significant ($p<0.05$) compared with the control

Antiarrhythmic activity in models of atrial cardiac rhythm disturbances

The influence on the effective refractory period of the isolated atrial appendages of a guinea pig

As a result of the conducted studies, it was established that SS-68 caused an increase in the effective refractory period of the isolated atrial appendage. When compared with the known antiarrhythmic drugs, it turned out that SS-68 exceeded amiodarone, lidocaine and quinidine 2.8, 2.5 and 10.4 times, respectively, but was 1.7 times inferior to ethacizine (Tab. 1, Fig. 12).

Table 1. Antiarrhythmic Effect of comp. SS-68 Expressed in Effective Concentration (EC_{15}), in Comparison with Some Antiarrhythmic Drugs, and in Relative Units, Where Amiodarone is Taken as the Reference Preparation.

Substance	Antiarrhythmic effect	
	EC_{15}[1] (M/l) and confidence limits at $p = 0.05$	in relation to amiodarone
SS-68	4.10×10^{-7} $2.92 \times 10^{-7} \div 5.28 \times 10^{-7}$	2.8
Ethacizine[2]	2.40×10^{-7} $1.70 \times 10^{-7} \div 3.10 \times 10^{-7}$	4.8
Quinidine[3]	4.26×10^{-6} $4.11 \times 10^{-6} \div 4.39 \times 10^{-6}$	0.27
Lidocaine	$1{,}02 \times 10^{-6}$ $0.84 \times 10^{-6} \div 1.20 \times 10^{-6}$	1.1
Amiodarone	1.15×10^{-6} $0.84 \times 10^{-6} \div 1.46 \times 10^{-6}$	1.0

Note: [1]EC_{15} – effective concentration of the substance, increasing the refractory period by 15%;
[2] – Tikhonova 1990;
[3] – Sirotenko 2003.

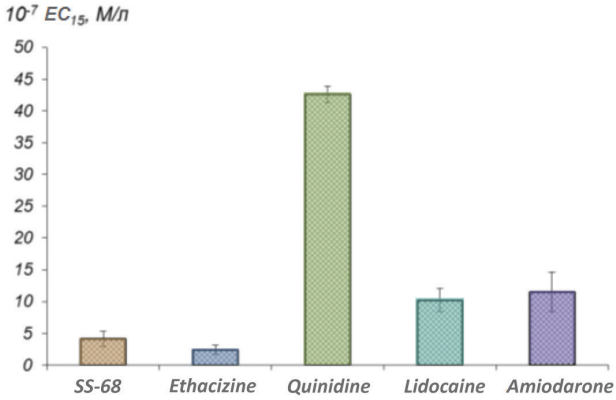

Figure 12. Comparative activity (according to EC_{15}) of SS-68, ethacizine, quinidine, lidocaine and amiodarone in their effect on the effective refractory period of the isolated atrial appendage of a guinea pig. Note: EC_{15} – effective concentration of the substance, increasing the refractory period by 15%.

The influence on atrial flutter induced by mechanical destruction of the sinus node and subsequent electrostimulation of the atria in dogs

The conducted studies showed that SS-68, at doses for antiarrhythmic activity (to arrest atrial flutter) expressed in mg/kg and mM/kg, exceeds quinidine, etmozine and amiodarone 12.4 and 5.4, 4.9, and 3.7, 5.1 and 2.5 times, respectively (Tab. 2, Fig. 13).

Table 2. Antiarrhythmic Effect of SS-68, Quinidine, Etmozine and Amiodarone When Administered Intravenously by the Method of Biological Titration in Conditions of Atrial Flutter in Dogs.

Substance	Dose to arrest atrial flutter		Antiarrhythmic effect in relation to amiodarone
	mg/kg	мM/kg	
SS-68	1.86±0.24*	0.0055	5.05/2.51
Quinidine	23.0±1.25[2]	0.0296	0.41/0.47
Etmozine	9.2±1.67[2]	0.0204	1.02/0.68
Amiodarone	9.4±0.6	0.0138	1.0/1.0

Note: * – $p<0.001$ relative to all the reference drugs.
[1] – in the numerator – relative to the dose of amiodarone, expressed in mg/kg, in the denominator – in mM/kg;
[2] – Senova 1973;
[3] – Dolskaya 2010.

With atrial flutter along the mechanical destruction of the sinus node and subsequent electrostimulation of the atria in dogs, SS-68 by the antiarrhythmic activity exceeds etmosin and amiodarone almost in the same way, and quinidine – to a greater extent.

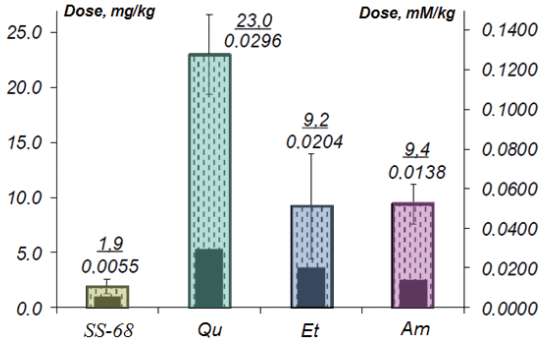

Figure 13. Comparative activity of SS-68, quinidine (Qu), etmozine (Et) and amiodarone (Am) in dogs with atrial flutter. Note: bar charts: shaded bars – doses in mg/kg, dark bars – doses in mM/kg; figures above the bars: in the numerator – doses in mg/kg, in the denominator – doses in mM/kg. The data characterizing quinidine and etmozine are given according to (Senova et al. 1973), amiodarone – according to (Dolskaya 2010).

The influence on fibrillation of atria induced by their paired stimulation on the background of vagal heart failure initiated by tonic stimulation of the vagus nerve in cats

SS-68 at a dose of 20 μg/kg 5, 30, 60 and 120 min after intravenous administration caused a significant decrease in the duration of atrial fibrillation (AF) by 54, 38, 35 and 33%, respectively. Along with this, the tonic component of the chronotropic effect of the vagus nerve (VN) decreased by 38, 29, 15 and 20%, respectively.

As for the P-P and P-Q ECG intervals, the atrial excitation threshold, the effective refractory period, the sinoatrial conduction of excitation, the VN stimulation threshold and the synchronizing component of the chronotropic effect of VN, they did not undergo significant changes (Tab. 3).

At a dose of 50 μg/kg 5, 30, 60 and 120 min after intravenous administration, SS-68 compound induced a significant decrease in the duration of AF by 85%, 73%, 50% and 33%, respectively.

SS-68 exerted a vagolytic effect, which was evident in a significant increase in the stimulation threshold of VN by 16% (by the 5th minute of the study), synchronizing and tonic components of the chronotropic effect of VN by 50% and 47%, 41% and 41%, 41% and 37%, 37% and 31%, respectively (by the 5th, 30th, 60th and 120th minutes of the study) (Tab. 3).

It should be noted that in 2 experiments out of 8, SS-68 did not cause the synchronizing component of the chronotropic effect of VN when compared to the baseline. With increasing the dose, of SS-68 to 250 μg/kg, after 5, 30, 60 and 120 min, a statistically significant decrease in the duration of AF was recorded – by 92%, 84%, 62% and 54%, respectively. The R-P and P-Q ECG intervals, as well as the effective refractory period, significantly increased: the first indicator – by 13%, 10% and 8% (by the 5th, 30th and 60th min), the second – by 22% and 14% (by the 5th and 30th min), the third – by 18%, 13% and 12% (by the 5th, 30th and 60th minutes of the study). The atrial excitation threshold and the sinoatrial conduction of excitation were virtually unchanged. Vagolitic activity of SS-68 compound clearly manifested itself in a significant increase in the threshold for stimulation of VN by 24% and 14% (by the 5th and 30th minutes) and inhibition of the synchronizing and tonic components of the chronotropic effect of this nerve by 62% and 58%, 60% and 52%, 58% and 44%, 56% and 42%, respectively (by the 5th, 30th, 60th and 120th minutes of the study) (Tab. 3). Niferidil, used as a reference drug, at a dose of 10 μg/kg 5, 30, 60 and 120 min after its intravenous administration caused a significant decrease in the duration of AF, which was 46%, 27%, 23% and 22%, respectively. In addition, there was a decrease in both the tonic and synchronizing components of the chronotropic effect of VN, while the P-P and P-Q ECG intervals, the atrial excitation threshold, the sinoatrial conduction of excitation and the VN stimulation threshold remained virtually unchanged from the baseline data. Thus, SS-68 compound in conditions of neurogenic AF, caused by stimulation of VN in cats, has a dose-dependent antiarrhythmic effect. SS-68 at a minimal antiarrhythmic dose (20 μg/kg), unlike niferidil (10 μg/kg), does not have a significant effect on the synchronizing component of the chronotropic effect of VN. By its antifibrillatory effect, SS-68 is inferior to niferidil.

The influence of SS-68 on the dynamics of the excitation foci (EF) in the sinoatrial node when stimulating the vagal nerve in cats

In anesthetized cats with an open thorax and pericardium, on controlled respiration, the initial heart rate was 172.3±1.2 bpm. In a high-frequency electric field, one EF with an area of 0.04±0.003 mm^2, localized at the opening

Table 3. Influence of SS-68 at Doses of 20, 50, 250 μg/kg on the Duration of Atrial Fibrillation Before and 5, 30, 60 and 120 Minutes After Administration of the drug (Reference Drug – Nifedipine at a Dose of 10 μg/kg).

Substance	Baseline	The duration of atrial fibrillation (% of the baseline)			
		5 min after drug administration	30 min after drug administration	60 min after drug administration	120 min after drug administration
SS-68 (20 μg/kg i/v)	208.0±26.0	95.0±19.0* (46.0%)	129.0±27.0* (62.0%)	136.0±26.0* (65.0%)	140.0±27.0* (67.0%)
SS-68 (50 μg/kg i/v)	140.0±7.0	21.0±4.0* (15.0%)	38.0 ± 6.0* (27.0%)	70.0 ± 12.0* (50.0%)	94.0 ± 14.0* (67.0%)
SS-68 (250 μg/kg i/v)	150.0±8.0	12.0±4.0* (8.0%)	24.0±5.0* (16.0%)	58.0±6.0* (38.0%)	70.0±6.0* (46.0%)
Niferidil (10 μg/kg i/v)	102.0±12.0	55.0±8.0* (54.0)	74.0±12.0* (73.0)	79.0±14.0* (77.0)	80.0±12.0* (78.0)

Note: * – the differences are statistically significant ($p<0.05$) compared to the baseline.

of the cranial vein, was visible. Under the microscope, the EF was not homogeneous and was like luminous pools (Tab. 4, Fig. 14).

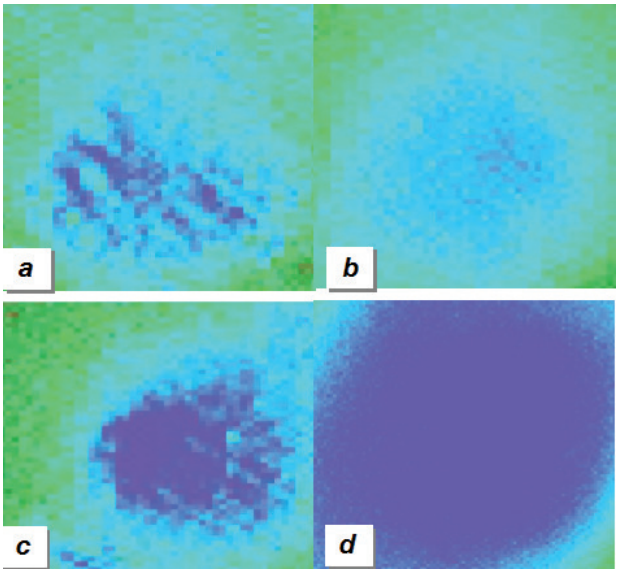

Figure 14. Influence of SS-68 on the EF (in blue) in the cat's SAN. Note: a – the initial state, b – with stimulating VN, c –45 minutes after the administration of SS-68; g – in 45 minutes with vagal-cardiac synchronization (VCS).

Table 4. Effect of SS-68 on the Dynamics of the Excitation Foci in the Sinoatrial Node when stimulating the vagus nerve in cats

Parameters	Initial	Bradicardia	After injection of SS-68
Heart rate	172.3±1.2	140.4±1.8 $p_1 = 0.01$	164.7±1.2 $p_2 = 0.01$ $p_3 = 0.01$
EF area, mm²	0.040±0.003	0.042±0.002 $p_1 > 0.05$	0.042±0.004 $p_2 > 0.05$ $p_3 > 0.05$
Vertical localization of the EF from the opening of the cava, mm	3.2±0.3	5.7±0.4 $p_1 = 0.01$	4.3±0.1 $p_2 = 0.01$ $p_3 = 0.01$
Horizontal localization of the EF from the edge of the cava, mm	1,0±0,2	1,8±0,1 $p_1 = 0,01$	1,0±0,2 $p_2 > 0,05$ $p_3 = 0,01$
In-depth localization of the EF from the edge of the node, mm	0.43±0.02	0.46±0.01 $p_1 > 0.05$	0.44±0.01 $p_2 > 0.05$ $p_3 > 0.05$
EF brightness histogram, bit	150.0±1.4	108±1.0 $p_1 = 0.01$	148.0±1.2 $p_2 = 0.01$ $p_3 = 0.01$
Minimum wavelength limit, nm	410±2,8	468±3,4 $p_1 = 0,01$	465,0±4,5 $p_2 = 0,01$ $p_3 > 0,05$
Maximum wavelength limit, nm	642.7±4.1	568±4.2 $p_1 = 0.01$	610.0±3.8 $p_2 = 0.01$ $p_3 = 0.01$
Range, nm	232.7±3.2	100.0±1.5 $p_1 = 0.01$	145.7±1.8 $p_2 = 0.01$ $p_3 = 0.01$
Wavelength median, nm	550.4±2.7	475.2±2.2 $p_1 = 0.01$	480.0±3.0 $p_2 = 0.01$ $p_3 = 0.01$

Note: p_1 – reliability factor between the data of columns 1 and 2: p_2 – reliability factor between the data of columns 1 and 3; p_3 – reliability factor between the data of columns 2 and 3

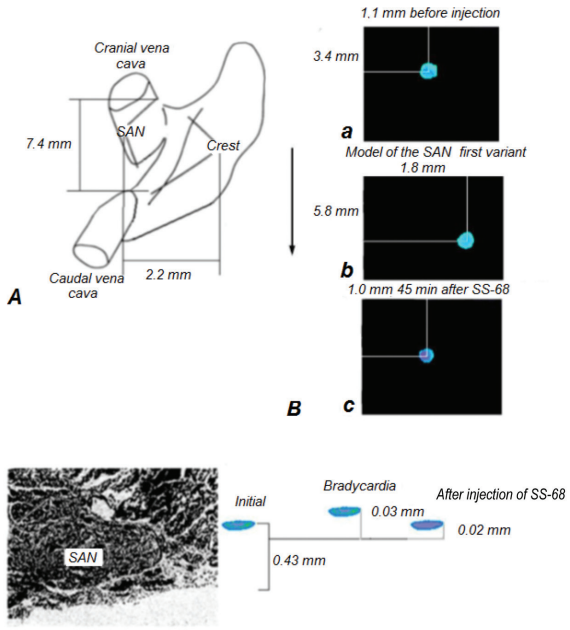

Figure 15. EF migration (blue against black background) of SAN in a cat. Note: A – the localization scheme for the cat's SAN. B – localization of the EF in the SAN: a – the initial EF localization; b – EF localization in case of bradycardia caused by stimulatng VN with electrical pulses in a batch mode; c – localization of the EF 45 minutes after the administration of SS-68. C – the morphological structure of the SAN (left) and the localization of the EF in the depth of the SAN (right).

The influence of SS-68 compound on cardiac rhythm disturbances of neurogenic origin

Antiarrhythmic activity in conditions of cardiac rhythm disturbances induced by injecting aconitine into the IV ventricle of the cat's brain

It was established that SS-68 compound, when used to arrest aconitine-induced arrhythmia of the central origin in experiments on cats, by its antiarrhythmic activity with ED_{50} expressed in mg/kg is more superior than amiodarone, etmozine, ethacizine and lidocaine, is inferior to anaprilin, and with ED_{50} expressed in mM/kg, it is more superior than amiodarone, lidocaine and etmozine and practically does not differ from anaprilin and ehtacizine. By TW, SS-68 is more significant than all the reference drugs (Fig. 16).

Antiarrhythmic activity in conditions of cardiac arrhythmias induced by injecting strophanthine K in the IV ventricle of the cat's brain

SS-68 compound, when used to arrest strophanthine-induced arrhythmia of central origin in experiments on cats, by antiarrhythmic activity is more significant than amiodarone, etmozine and lidocaine, is inferior to verapamil, anaprilin and ethacizine. By TW, SS-68 is more significant than anaprilin, ethacizine, etmozine and lidocaine, but is inferior to amiodarone and verapamil (Fig. 17).

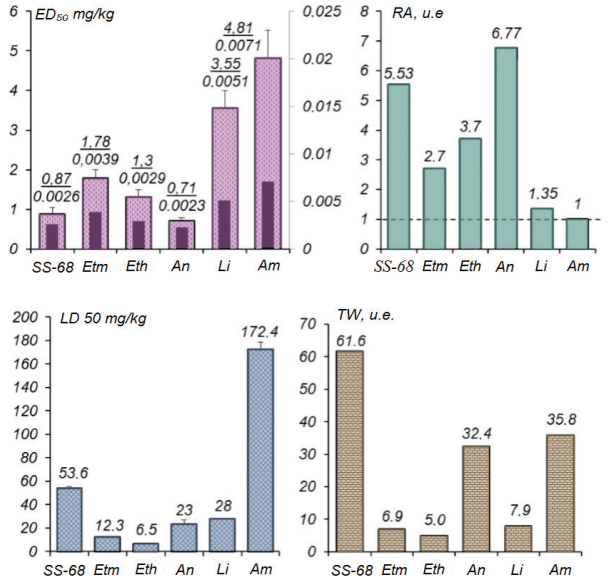

Figure 16. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) SS-68, etmozine (Etm), ethacizine (Eth), anaprilin (An), lidocaine (Li) and amiodarone (Am) used to arrest aconitine-induced arrhythmia of the central origin in experiments in anesthetized cats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA –relative activity; TW - therapeutic window

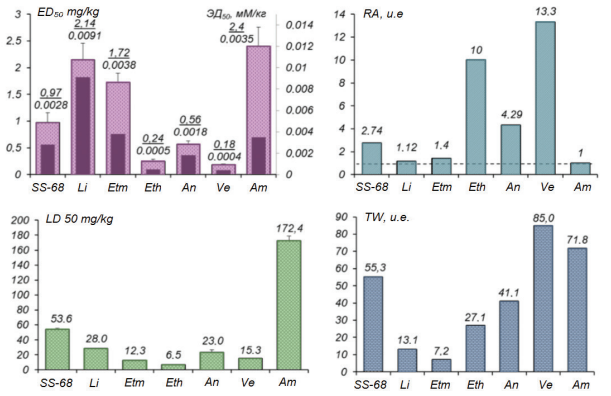

Figure 17. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68, lidocaine (Li), etmozine (Etm), ethacizine (Eth), anaprilin (An), verapamil (Ve) and amiodarone (Am) used to treat strophantine-induced arrhythmia of the central origin in experiments in anesthetized cats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW – therapeutic window

Antiarrhythmic activity in conditions of cardiac arrhythmias induced by injecting cesium chloride in the IV ventricle of the cat's brain

It was established that SS-68 compound, in conditions of cesium chloride- induced arrhythmia of the central origin in experiments in anesthetized cats, by its antiarrhythmic

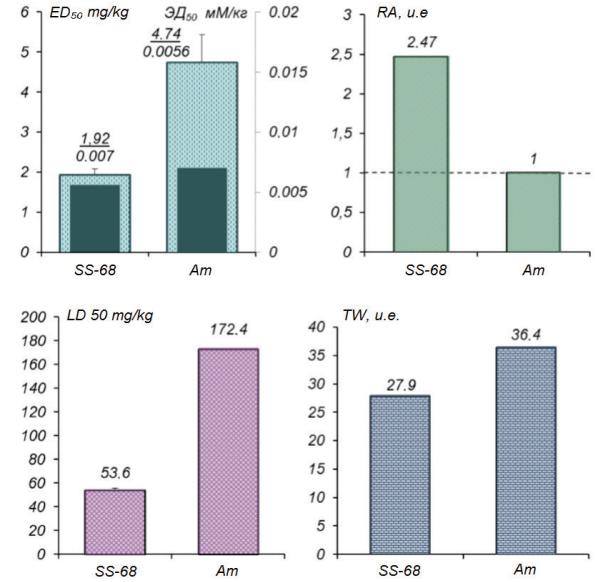

Figure 18. Comparative activity [according to ED_{50} in mg/kg (shaded bars) and mM/kg (dark bars)], relative activity (RA), acute toxicity (LD_{50}) and therapeutic window (TW) of SS-68 and amiodarone (Am) used to arrest cesium chloride- induced arrhythmia of central origin in experiments in anesthetized cats. Note: ED_{50} – effective dose; LD_{50} – dose that causes the death of 50% of animals; RA – relative activity; TW - therapeutic window

activity is more significant than amiodarone, and by TW, it is inferior to it (Fig.18).

The influence of SS-68 compound on the bioelectrical activity of the somatosensory cortex and cardiac arrhythmias caused by microapplication of carbachol on the cortical structures of the rat's brain

Injection of 29.3 μM of the SS-68 solution (marked by arrows in the Figure) suppresses epileptiform potentials induced by preliminary application of carbachol a few seconds after the artifact of the test substance microapplication. However, after a 10-minute observation, the epileptiform commissures adhesions are restored, which indicates a longer action of CCh than SS-68 compound (Fig. 19).

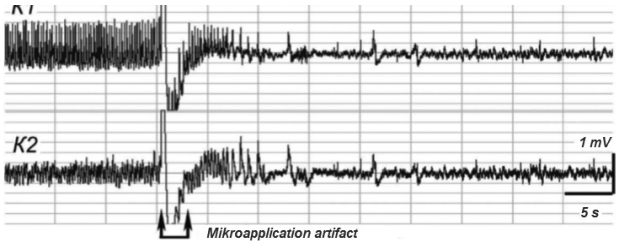

Figure 19. Oppressive effect of SS-68 compound (29.3 μM) on the epileptiform activity caused by the preliminary exposure to CCh (12.5 mM). Note: K1 and K2 – the upper (400 μm immersion depth) and the lower (1200 μm) layers of the cortex column, respectively, in which the microapplication of SS-68 was made. (up to 1 μl). The arrows mark the time of administration of SS-68.

In conditions of HRD induced by the application of CCh to the cortical structures of the brain of animals, SS-68 has a pronounced antiarrhythmic effect (Fig. 20), which is confirmed by the previously obtained data on the ability of this substance to stop the central HRD induced by the introduction of aconitine, strophanthine and cesium chloride into the IV ventricle of the cat's brain.

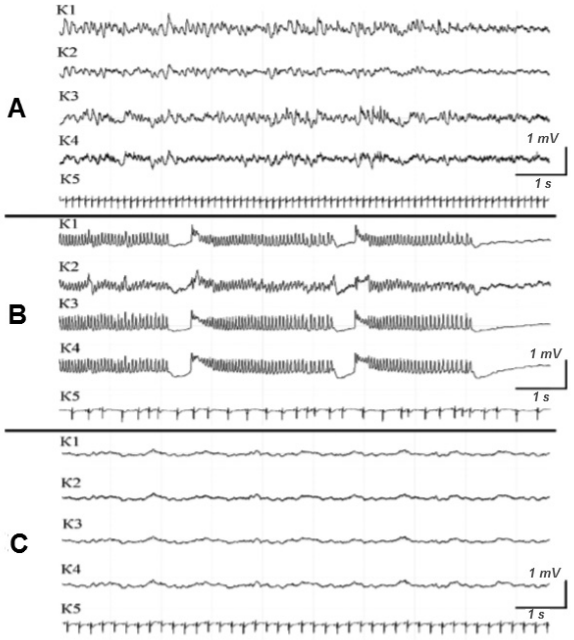

Figure 20. Antiarrhythmic effect of SS-68 in conditions of HRD induced by microapplication of CCh on the somatosensory cortex of the rat's brain. Note: K1 and K2 – the upper (400 μm immersion depth) and the lower (1200 μm) layers of the experimental cortical column, respectively, in which the microapplication was made (up to 1 μl) KX and the SS-68; K3 and K4 – upper (400 microns) and lower (1500 microns) layers of the control column located at a distance of 1200 microns from the experimental one; K5 – the electrocardiogram.

The effect of SS-68 on coronary circulation, contractile activity of the myocardium and general hemodynamics in conditions of intact myocardium

In experiments on cats in conditions of intact myocardium, SS-68 (2 mg/kg, intravenously) increases CAFV, reduces MOD and creates the oxygen reserve (OR) in the myocardium, reduces the rhythm of heartbeats, slightly reduces the excitation propagation velocity in the heart, reduces myocardial contractility, and increases the refractory period (Fig. 21).

The influence on coronary blood flow in dogs

In experiments on dogs, SS-68, when administered intracoronarily (0.05 mg), increases both diastolic (at the end of diastole) and systolic coronary blood flow (Fig. 22). At the same time, the contractility of the myocardium is somewhat reduced (trend).

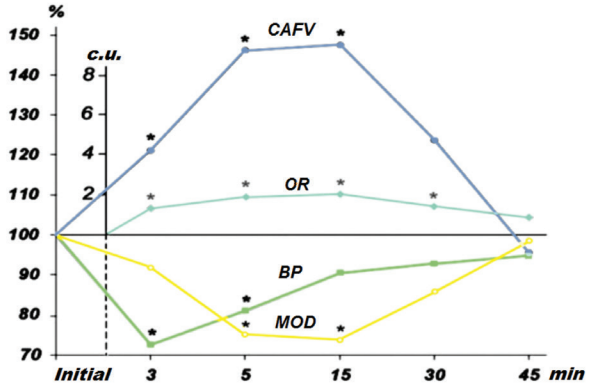

Figure 21. Influence of SS-68 (2 mg/kg intravenously) on the blood supply of the heart in cats. Note: curves from top to bottom: CAFV – coronary artery flow velocity, OR – oxygen reserve, BP – blood pressure, MOD – myocardial oxygen demand. * – significance in comparison with the initial data ($p<0.05$).

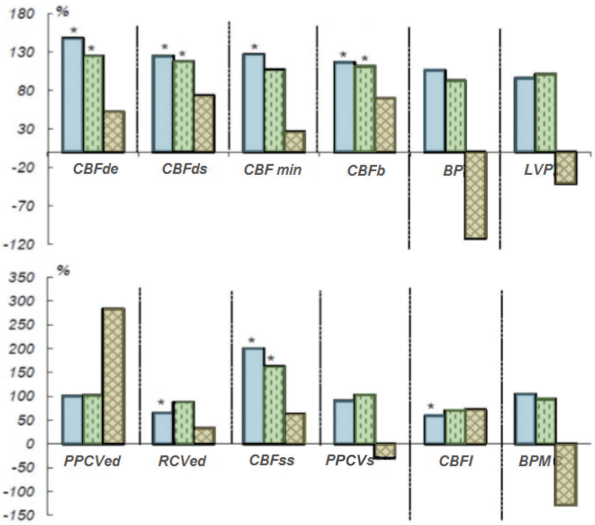

Figure 22. Influence of SS-68 (0.05 mg, intracoronarily) on the ***phasic coronary blood flow (PCBF)*** in dogs Note: Columns: 1, 2 and 3 – peak of reactive hyperemia (RH) (% of the initial data), peak of the action of SS-68 (% of the initial data) and the expansion reserve (% of RH), respectively. CBFed – coronary blood flow (CBF) at end diastole; CBFds – CBF diastolic stroke; CBF min – diastolic CBF per minute; CBFb. – CBF per beat; BP – blood pressure; LVP – left ventricular pressure; PPCVed – perfusion pressure in the coronary vessels at end diastole; RCVed – resistance of coronary vessels at end diastole; CBFss – CBF systolic stroke; PPCVs – perfusion pressure in the coronary vessels systolic; CBFI – CBF index; BPM – beats per minute (heart rate). * – the differences are statistically significant ($p<0.05$) compared to the baseline data.

The influence of SS-68 compound on coronary circulation, contractile myocardial activity and general hemodynamics in conditions of ischemic myocardium

The influence of SS-68 compound on the coronary artery flow velocity, cardiac activity and hemodynamics in ischemic myocardial conditions in dogs.

It was established that under conditions of ischemic myocardial damage caused by occlusion of LAD, SS-68 (2 mg/kg, intravenously) statistically significantly increased (compared with the data received about prior and post-occlusion of LAD) CAFV 15.5% and 26.0%, 54.2% and 68.1%, 36.5% and 48.9%, 17.8% and 28.5% after 5, 10, 15, 30 and 45 minutes, respectively. At the same time, MV, SV, BP, dp/dt+, dp/dt- and heart rate (compared with those after 10 min of occlusion of LAD) showed a tendency to decrease. A certain exception was BP, which by the 45th minute of the study had decreased statistically significantly in comparison with the baseline data (before CAO) (Fig. 23, Fig. 24).

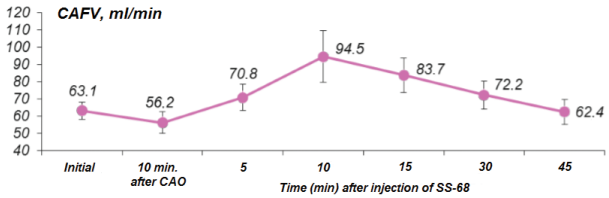

Figure 23. Influence of SS-68 (2 mg/kg, intravenously) on the coronary artery blood flow velocity (CAFV) in conditions of myocardial ischemia induced by occlusion of the coronary artery (CAO) in dogs.

Thus, SS-68 compound, when administered intravenously at a dose of 2 mg/kg in experiments in dogs, increases collateral circulation in the myocardial ischemia focus, reduces myocardial oxygen demand, reduces blood pressure and heart rate (trend).

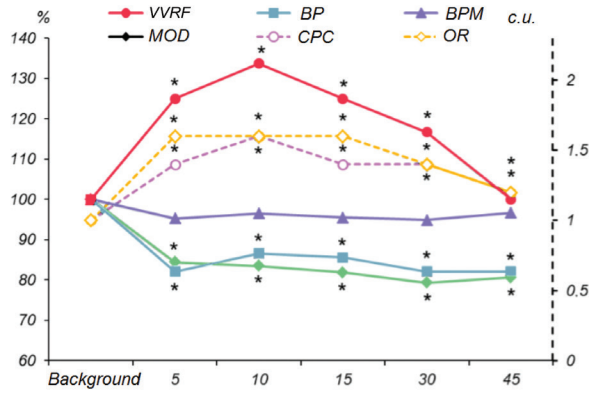

Figure 24. Influence of SS-68 compound (2 mg/kg, intravenously) on the blood supply of the myocardial ischemia focus in dogs. Note: VVRF – volume velocity of the retrograde blood flow; MOD (DP) – double product [index of myocardial oxygen demand (MOD)]; BP – blood pressure; OR – oxygen reserve; BPM – beats per minute (heart rate); * – the differences are statistically significant (p<0.05).

The influence on coronary circulation in conditions of myocardial ischemia induced by pituitrin in experiments in cats.

As a result of the conducted experiments, it was found that intravenous administration of pituitrin at a dose of 5 units/kg to the control animals (n=9) induced (by the 5th minute) in the majority of them a decrease in CAFV (by 25.6%, p<0.05) and a slight increase in BP (4.9%, p>0.05). At the same time, MOD increased slightly (by 6.4%, p> 0.05), and OR decreased (by 30%, p<0.001). In 322 other cats (n=4), on the contrary, there was an increase in CAFV (by 8-15%), along with an increase in MOD and BP (by 3.0-3.5 and 15-20%, respectively) (Fig. 25).

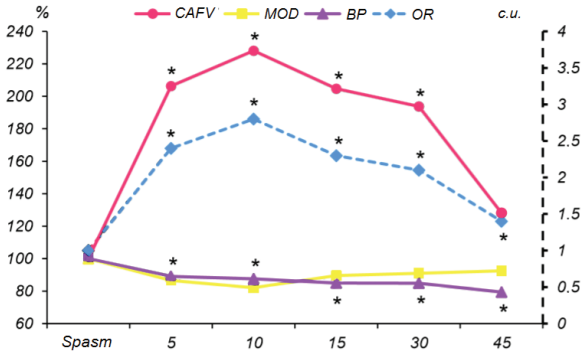

Figure 25. Changes in indices in relation to the baseline data 5 min after pituitrin-induced coronary spasm along with administration of SS-68 compound (2 mg/kg, intravenously) in cats. Note: CAFV – coronary artery blood flow velocity, MOD – myocardium oxygen demand, BP – blood pressure, OR – oxygen reserve. * – the differences are statistically significant (p<0.05).

The influence of SS-68 compound on the functional state of the focus of myocardial ischemia in cats

It was established that preventive intravenous administration of SS-68 at a dose of 1 mg/kg increased the resistance of the myocardium to ischemia induced by occlusion of LAD, causing depression of ΣST in a most pronounced way (by 20.9%, 18.5%, 24.1%, 25.3% and 21.0%) 3 min after injection of the test substance (at the 0.5th, 1st, 2nd, 3rd and 4th minutes of CAO). The duration of the action was 20 minutes (Fig. 26).

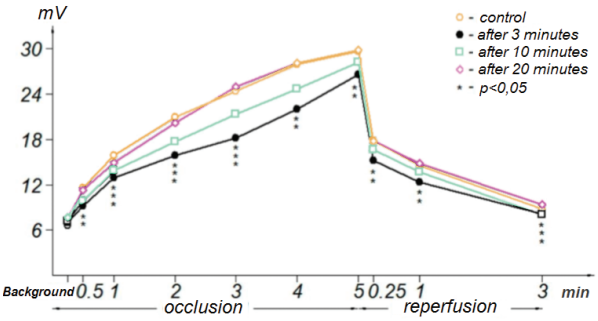

Figure 26. Antianginal activity of SS-68 compound (1 mg/kg, intravenously) in experiments in cats. Note: * – the differences are statistically significant (p<0.05).

With increasing a dose of SS-68 to 2 mg/kg, the most significant ST-segment depression also occurred on the 3rd

minute after the administration of the substance and was 34.3%, 40.5%, 39.2%, 35.2%, 33.8% and 29.2% at the 0.5th, 1st, 2nd, 3rd, 4th and 5th min after CAO (Fig. 27). The duration of the action was 40 minutes.

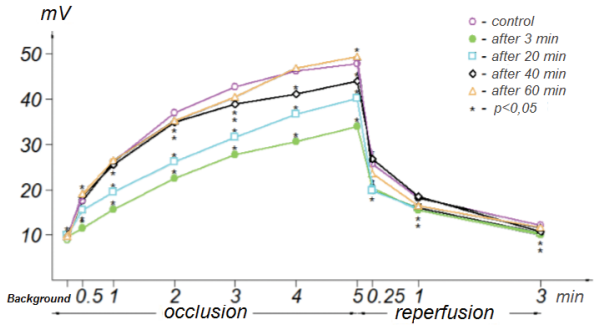

Figure 27. Antianginal effect of SS-68 comound (2 mg/kg, intravenously) in experiments in cats. Note: * – the differences are statistically significant ($p<0.05$).

The effect of SS-68 on the size of the necrotic zone (NZ) in experimental myocardial infarction in cats

It was found that with a double intravenous injection of SS-68 at a dose of 2 mg/kg (the total dose of 4 mg/kg) showed a statistically significant decrease in the necrotic zone (NZ) in experimental MI. While in the control series

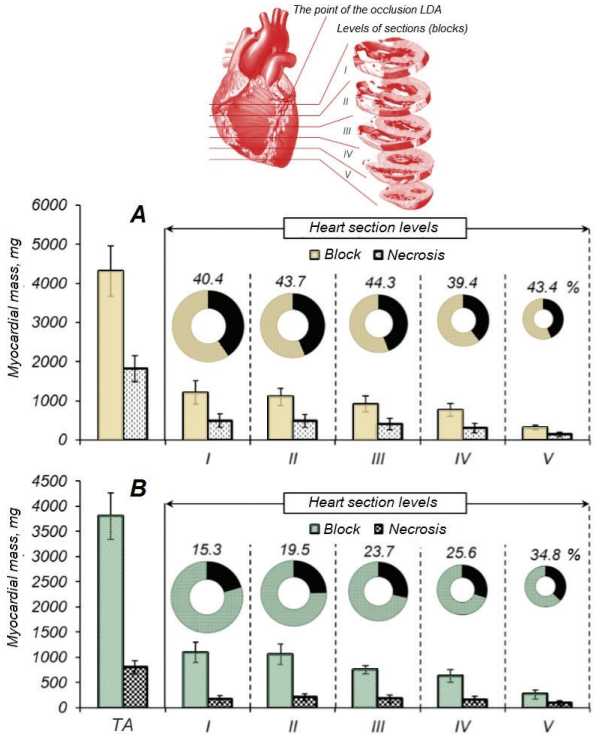

Figure 28. Influence of a double intravenous administration of SS-68 compound at a dose of 2 mg/kg (the total dose of 4 mg/kg) on the size of the necrotic zone (in %) 24 hours after the experimental myocardial infarction in cats. Note: A – control, B – after administration of SS-68. TA – total amount ; I, II, III, IV, V – levels of sections (blocks) of the heart.

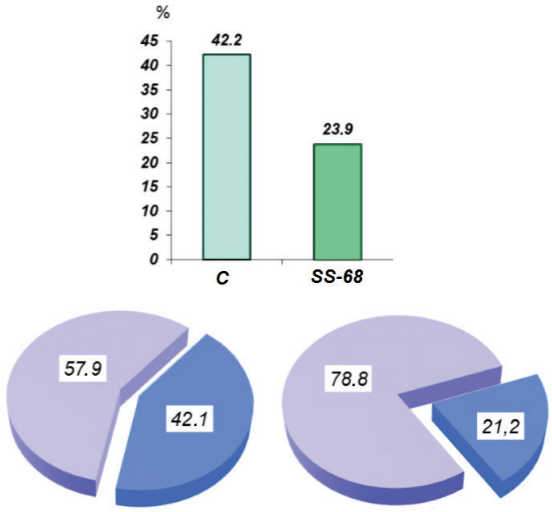

Figure 29. Average mass of necrotic myocardium: in control (C) and under the influence of SS-68 compound (bar chart); total index of necrosis (in %) (pie chart, necrosis – darker sector).

of experiments, the left ventricular NZ was 42.1%, in the experimental series – 21.2%, i.e., 49.6% less. When analyzing the protective effect of SS-68 by the levels of myocardial sections, it turned out that the restriction of NZ is most significant at level I (62.1% less than in control), then at II, III, IV and V levels (by 55.4%, 46.5%, 35.0% and 19.8% less, respectively) (Fig. 28, Fig. 29).

Discussion

To date, there have been significant achievements of Russian and foreign pharmacologists, chemists and clinicians in creating and introducing into the practical medicine a number of antiarrhythmic drugs different by their chemical structure, nature, spectrum, activity and mechanism of action; nevertheless, one of the most important tasks of modern pharmacology is searching for and developing new highly active substances of the corresponding action (Kaverina 1986, Mashkovsky 1998, Yaroshevsky Gatsura 2011, Galenko-Yaroshevsky et al. 2012a, 2012b, 2012c, 2012d). This is due to the fact that HRDs often accompany many diseases: IHD and its complications (MI, acute and chronic HF), acquired and congenital heart defects, cardiomyopathies, myocarditis, exogenous intoxications and endogenous metabolic disorders in renal, hepatic and respiratory insufficiencies (Golitsyn 2008, Karpov and Sorokin 2012, Tiso et al. 2001).

In the present study, the antiarrhythmic and antianginal properties of a new indole derivative – SS-68 compound – were studied in detail. The models chosen cover a wide range of pathological conditions that can be extrapolated to most of the nosological forms found in clinical practice.

So, in cardiogenic arrhythmias, it was established that:

– *under conditions of by aconitin-induced HRDs in experiments in conscious rats*, SS-68 by antiarrhythmic activity, with ED_{50} expressed in mg/kg, is comparable

with lidocaine and is superior to amiodarone, and in experiments in anesthetized rats, SS-68 by antiarrhythmic activity and TW is superior to lidocaine, amiodarone, aymalin, and quinidine. The aconitine model of arrhythmia is associated with disruption of Na^+ channels. Under the conditions of this model of arrhythmia, antiarrhythmic drugs belonging to the first class, which tend to block Na^+-channels, have the most pronounced activity (Filippova et al. 2003, Galenko-Yaroshevsky et al. 2012c);

– *in calcium chloride-induced arrhythmia model in experiments in conscious rats,* SS-68 (ED_{50} in mg/kg) by anti-arrhythmic activity is superior to lidocaine and amiodarone, but inferior to verapamil; it has a larger TW than reference drugs. In conditions of *calcium chloride-induced* arrhythmia, the effect of excess Ca^{2+} induces depolarization of cardiomyocytes, which leads to the appearance of ectopic foci of automatism and micro re-entry and, as a consequence, to the cardiac VF. In this model of arrhythmia, antiarrhythmics of the IV class and, to a lesser extent, of the I and II classes, show the greatest activity (Filippova et al. 2003, Galenko-Yaroshevsky et al. 2012c);
– *in barium chloride-induced arrhythmia in experiments in conscious rabbits,* SS-68 (ED_{50} in mg/kg) by antiarrhythmic activity and TW is superior to amiodarone and, to a greater extent, to quinidine. In this experimental model, there is selective blockage of Ba^{2+} I_{K1}-channels, prolongation of effective refractory period (ERP) of the ventricles of the heart, which leads to an increase in the level of Ca^{2+} in cardiomyocytes in AP, possibly, in RP (resting potential) (Filippova et al. 2003, Dorian et al. 1996). In this HRD model, the most significant effect is exerted by blockers of K^+-channels and β-adrenoblockers;
– *when preventing cesium chloride-induced arrhythmia* in experiments in anesthetized rats, SS-68, with ED_{50} expressed in mg/kg, by its antiarrhythmic activity is superior to amiodarone. In cases of arresting cesium chloride-induced arrhythmia, SS-68, with ED_{50} expressed both in mg/kg and mM/kg, by its antiarrhythmic activity is superior to amiodarone, but and does not differ from it in terms of TW. This model is characterized by a disruption in the functioning of transmembrane potential-dependent K^+-channels, and in this case, antiarrhythmic drugs of the third class are most effective (Galenko-Yaroshevsky et al. 2012c, Isenberg 1976, Jones et al. 2001);
– *in adrenaline-induced arrhythmia* in experiments in anesthetized rats, SS-68 by its antiarrhythmic activity is superior to amiodarone (with ED_{50} expressed as in mg/kg) or comparable to it. This HRD model is specific for antiarrhythmics of classes II, and also IV (Filippova et al. 2003, Galenko-Yaroshevsky et al. 2012c);
– *in strophanthine-induced arrhythmia* in experiments in anesthetized cats, SS-68 (with ED_{50} expressed in mg/kg and mM/kg) by its antiarrhythmic activity is superior to lidocaine and quinidine, but inferior to aymalin and verapamil. In strophantine-induced arrhythmia, strophanthine increases the trigger activity of cardiomyocytes, which causes the appearance of heterotrophic foci of excitation in the myocardium. In this HRD model, antiarrhythmics of classes I and II are most effective (Filippova et al. 2003, Galenko-Yaroshevsky et al. 2012c).
– *in ventricular arrhythmia induced by a two-stage coronary artery ligation* in experiments in dogs, SS-68 has an antiarrhythmic effect, significantly exceeding lidocaine. In ventricular arrhythmia induced by occlusion of LAD, antiarrhythmic effect is mainly exerted by the substances belonging to class I (Galenko-Yaroshevsky et al. 2012c).
– *in paired stimulation of the atria in conditions of vagal blockade* in cats, SS-68 eliminates AF. However, by antifibrillatory action in the experimental conditions, SS-68 is inferior to niferidil. In conditions of VF induced by applying the electrostimulation to the vulnerable period of the cardiac cycle, the drugs of classes I and III have an antiarrhythmic effect (Galenko-Yaroshevsky et al. 2012c).
– *in conditions of ventricular HRD* induced by experimental MI (dogs), SS-68 compound by its the ability to completely stop ectopic contractions of ventricles and by the total duration of antiarrhythmic action exceeds lidocaine 5 times.
– *in experiments on the isolated atrial appendage of the guinea pig's heart,*. SS-68 increases myocardial ERP, exceeding in this respect amiodarone, lidocaine and quinidine, but but being inferior to ethacizine.

In neurogenic HRD, we found that:

– *in aconitine-induced arrhythmia* in experiments in cats, SS-68 by its antiarrhythmic activity, with ED_{50} expressed in mM/kg, exceeds amiodarone, lidocaine and etmozine and almost does not differ from anaprilin and ethacizine; but by TW, it is more significant than all the reference drugs;
– *in strophanthine-induced arrhythmia* in experiments in cats, SS-68 by its antiarrhythmic activity is superior to amiodarone, etmozine and lidocaine; however, it is inferior to verapamil, anaprilin and ethacizine; by TW, it is more significant than anaprilin, ethacizine, etmozine and lidocaine, but is inferior to amiodarone and verapamil;
– *in cesium chloride-induced arrhythmia* in experiments in cats, SS-68 by its antiarrhythmic activity is superior to amiodarone, but is inferior to it by TW;
– *in carbachole-induced arrhythmia* in experiments in rats, SS-68 exhibits a pronounced antiarrhythmic effect, exerts a depressing effect on the background focal rhythmogenesis of SSC of animals, suppresses the epileptiform activity of cortical structures.

When studying the antianginal properties and the effect on coronary blood flow, it was established that:

– under conditions of both intact (cats, dogs, rats) and ischemic (dogs) myocardium, SS-68 compound increases the CAFV, creates additional OR in the myocardium, reduces BP and, to a lesser extent, reduces myocardial contractility, and increases collateral circulation in an ischemic focus;
– in *pituitrin-induced coronarospasm* (cats), SS-68 compound increases CAFV, increases heart OR, reduces MOD (trend) and blood pressure; SS-68 exerts an antianginal effect (rabbits, cats) and in this respect is comparable to amiodarone (by decreasing the ST interval) or exceeds it (by the duration of action), but is inferior to anaprilin; it reduces myocardial NZ, surpassing amiodarone and, to a greater extent, anaprilin.
– *with a double intravenous injection,* SS-68 by its ability to limit NZ under conditions of experimental MI in cats is superior to or comparable to that of amiodarone and is more effective than anaprilin

Conclusions

Thus, SS-68 compound is a promising pharmacological agent with a high preventive and arresting effects towards various electrophysiological disorders in the heart, and, in addition, it has significant antiischemic and coronary vasolidating properties. Special attention should be paid to an in-depth study of the molecular mechanisms of action of this compound.

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