Effect of Imidazobenzoimidazole Derivatives RU-353, RU-563, and Lidocaine on Cerebral Circulation in Rats

A. P. Galenko-Yaroshevskii*, A. Yu. Turovaya, A. V. Uvarov, A. K. Prikhod'ko*, M. N. Ivashev, A. V. Arl't**, and V. A. Anisimova*****

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We demonstrated a dose-dependent inhibitory effect of novel imidazobenzoimidazole derivatives RU-353 and RU-563 on cerebral blood flow and systemic blood pressure in narcotized rats. The effects of RU-353 increased, while the effect of RU-563 decreased with increasing the dose.

Key Words: *imidazobenzoimidazole derivatives; cerebral circulation; systemic blood pressure*

Complexity, variability, and wide spread of cardiac rhythm disturbances on the one hand, and clinician dissatisfaction of modern drugs used for correction of arrhythmia, on the other, prompted the search for new agents with pronounced antiarrhythmic activity [4]. At present, pharmacologists and chemists focus on imidazobenzoimidazole (IBI) derivatives, which possess antiarrhythmic and hypotensive properties. A promising agent of this class is RU-353 (laboratory code) synthesized at the Research Institute of Physical and Organic Chemistry, Rostov State University. Its antiarrhythmic effects were examined on the models of peripheral [7,8] and central [9] arrhythmias. To elucidate possible mechanisms of the central action of RU-353, pharmacological analysis of its effects on adrenergic, cholinergic, and serotoninergic neurotransmitter systems in various regions of the brain was carried out [2]. There are no data on the effect of IBI on cerebral blood flow, although the disturbances in cerebral circulation are common complications of cardiac arrhythmia and arterial hypertension.

Kuban State Medical Academy, Krasnodar; *Krasnodar Regional Research Medical Center; **Pyatigorsk State Pharmaceutical Academy; ***Research Institute of Physical and Organic Chemistry of Rostov State University

The concurrent positive therapeutic action on cerebral vascular bed is a vital additional property of cardiotropic preparations [5]. Thus, our aim was to study the effect of RU-353, an IBI derivative, its bromine analog RU-563, and lidocaine (reference drug) on cerebral blood flow (CBF) in rats. Lidocaine was chosen due to pronounced local anesthetic properties of RU-353 [1], which can be considered as a class IB antiarrhythmic according to Vaughan-Williams nomenclature [10].

MATERIALS AND METHODS

The experiments were carried out on male Wistar rats (n=48) after a two-week quarantine. The animals were kept on unrestricted food and water under standard vivarium conditions. The rats were narcotized with sodium ethaminal (30-40 mg/kg, [2,3]).

Changes in CBF (ml/100 g per 1 min) were measured by hydrogen clearance [3,5,6].

The examined substances (laboratory codes RU-353 and RU-563) were injected intravenously in doses of 0.125 and 0.25 mg/kg, respectively. Lidocaine (12 mg/kg, intravenously) was used as the reference drug [5]. The control rats were injected intravenously with an equivalent volume of physiological saline.

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TABLE 1. Effect of RU-353, RU-563, and Lidocaine on Cerebral Blood Flow in Narcotized Rats (*M*±*m*, *n*=8)

Substance and dose (mg/kg)		Initial values	Changes (% of initial level)			
			5-15 min	30 min	45 min	60 min
Control		108.3±3.2	-0.9±0.7	-0.5±1.8	-1.3±1.8	-1.2±1.1
RU-353	0.125	122.6±18.6	-9.7±8.5	-3.4±4.5	-4.5±4.6	-11.7±1.5
	0.25	120.2±11.6	-14.7±3.8*	-14.9±2.7*	-7.7±1.9*	-1.6±8.6
RU-563	0.125	156.0±9.8	-25.0±5.5*	-41.3±6.8*	-20.8±6.8*	-9.5±1.1*
	0.25	116.8±4.5	-8.6±2.3	-0.2±0.9	-10.3±4.5*	-10.7±6.4
Lidocaine, 12		135.1±8.4	-35.2±3.4*	-33.8±5.5*	-48.1±3.1*	-43.8±7.9*

Note. Here and in Table 2: *$p<0.05$ compared to initial values.

TABLE 2. Effect of RU-353, RU-563, and Lidocaine on Systemic Blood Pressure in Narcotized Rats (*M*±*m*, *n*=8)

Substance and dose (mg/kg)		Initial values	Changes (% of initial level)			
			5-15 min	30 min	45 min	60 min
Control		121.5±8.5	0	-0.9±0.9	-1.2±1.3	-2.0±1.2
RU-353	0.125	110.4±13.2	-6.4±5.5	-10.6±6.8	-11.5±7.3	-16.5±9.6
	0.25	104.5±10.1	-9.6±4.6	-13.4±3.2*	-15.4±4.5*	-17.5±6.6*
RU-563	0.125	115.0±7.6	-10.5±2.4*	-10.5±5.4*	-19.6±4.1*	-20.5±6.3*
	0.25	120.8±9.5	-4.5±1.8	-0.5±1.8	-1.5±1.7	-3.2±2.4
Lidocaine, 12		124.5±5.6	-21.2±3.5*	-24.4±9.3*	-26.4±7.6*	-30.5±7.6*

RESULTS

In the control series, physiological saline produced no significant changes in CBF and systemic blood pressure (SBP) over 60 min (Tables 1 and 2).

RU-353 produced a dose-dependent decrease in SBP and CBF, although the effects were significant only when the dose was 0.25 mg/kg. The maximum decrease in CBF (by 14.7-14.9%) was observed during the first 30 min postinjection, but to minute 45 this decrease became virtually 2-fold less pronounced (the drop in CBF was 7.7%), and no significant changes in CBF were observed on minute 60 postinjection. It is noteworthy that SBP persistently dropped during the entire observation period (by 9.6-17.5% from minute 5 to minute 60, respectively). Maximum changes in CBF accompanied by minimum shifts in SBP confirm the hypothesis that the decrease in CBF does not results from the drop in SBP, and rather reflects the action of RU-353 on tuning of the autoregulatory mechanisms of cerebral blood vessels tone.

RU-563 injected in a dose of 0.125 mg/kg decreased CBF. The maximum effect (41.3%) was observed on minute 30 postinjection. The effect decreased during the following 30 minutes, but remained significant. SBP decreased monotonously by 10.5-20.5% from minute 5 to minute 60, respectively. Similarly to the previous case, there was no correlation between the changes in SBP and CBF.

In a higher dose of 0.25 mg/kg, RU-563 insignificantly decreased both SBP and CBF.

During the entire observation period (60 min) lidocaine (12 mg/kg) produced a significant decrease in SBP and CBF. The maximum drops in CBF (by 48.1%) and in SBP (by 30.5%) occurred on minute 45 and 60 postinjection, respectively. It should be noted that the lidocaine-induced changes in SBP and CBF were similar, which suggests the dependence of CBF on SBP shifts.

Thus, a novel spectrum of pharmacological activity of IBI derivatives RU-353 and RU-563 was demonstrated: both agents decreased CBF and SBP, which could be a valuable supplementary cardiotropic feature of these agents. Specifically, during hypertension stroke often accompanied by cardiac rhythm disturbances the use of antiarrhythmic preparations reducing SBP and CBF can be extremely reasonable, when pronounced increase in SBP is accompanied by breakdown of CBF regulation, which enhances the risk of cerebral edema due to congestion.

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