Effects of Bradysole and Dibasole on Cerebral Bloodflow under Experimental Conditions

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Bradysole (1 mg/kg intravenously) induced a moderate increase in cerebral bloodflow and a minor decrease in systemic blood pressure in narcotized rats. These effects were less pronounced compared to the effects of dibasole (bradysole structural analog) in the same dose.

Key Words: *bradysole; dibasole; cerebral bloodflow; systemic arterial pressure*

"Specific bradycardic agents" acting through chlorine channel blockade attract much recent attention in cardiopharmacology [3]. These substances reduce heart rate by directly affecting sinus node pacemaker cells and have virtually no effects on hemodynamic parameters. Bradysole, 2-mercaptobenzimidasole derivative [2] synthesized at the Institute of Pharmacology, Russian Academy of Medical Sciences, is a representative of this group of drugs. Antiarrhythmic effects of bradysole were studied on the models of cardiac arrhythmias; its antiischemic effect is also known [2,8]. Central sympathoinhibitory effect of bradysole was described [7], as well as its effects on the content of adrenergic, cholinergic, and serotoninergic neurotransmitters in different compartments of the brain [1]. The effects of bradysole on the central neurotransmitter systems prompted investigation of its effects on cerebral circulation and compare it with the effect of its structural analog dibasole.

MATERIALS AND METHODS

Experiments were carried out on 32 male Wistar rats (250-280 g) narcotized with sodium ethaminal (30-40 mg/kg intravenously) [5,6]. The animals were kept under common vivarium conditions on standard fodder with free access to water and food. Volume rate of cerebral bloodflow (CB) was studied by the hydrogen clearance method [5,6] based on evaluation of the velocity of hydrogen protons clearance from the cerebral tissue.

The sagittal sinus area was prepared and a platinum electrode was inserted at the site of sinus discharge. An indifferent electrode was placed on rat tail. Hydrogen was let into the trachea through a polyethylene tube during 1-2 respiratory movements. Systemic blood pressure (SBP) was measured in the right carotid artery with a mercuric manometer.

Bradysole was injected in doses of 0.5 and 1.0 mg/kg intravenously, dibasole 0.1 mg/kg intravenously. Control animals were injected with the same volume of saline.

RESULTS

No appreciable changes in CB and SBP were noted throughout the experiment (60 min) after injection of normal saline (Tables 1, 2).

Bradysole in a dose of 0.5 mg/kg had no significant effects on CB and SBP. In a dose of 1.0 mg/kg bradysole caused a transient moderate increase in CB starting from the 30th (by 9%) through 40th min (by 6.2%) postinjection; CB level decreased and virtually did not differ from the basal level by min 60 of the study. This was paralleled by a gradual decrease of SBP during the entire period of observation (by 6.4-9.6% from min 5 till min 60, respectively). The de-

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TABLE 1. Effects of Bradysole and Dibasole on CB in Narcotized Rats (*M*±*m*, *n*=8)

Drug, dose	Initial values	Shift, %			
		min 5-15	min 30	min 45	min 60
Control	108.3±3.2	-0.9±0.7	-0.5±1.8	-1.3±1.8	-1.2±1.1
Bradysole, 0.5 mg/kg	120.2±11.6	-1.3±5.4	2.8±1.8	1.7±1.3	1.2±1.0
Bradysole, 1.0 mg/kg	126.0±4.0	3.5±3.4	9.0±3.0*	6.2±1.8*	1.8±1.7
Dibasole, 1.0 mg/kg	107.4±6.2	12.7±3.6*	17.8±4.8*	25.7±3.3*	21.8±6.6*

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

TABLE 2. Effects of Bradysole and Dibasole on SBP in Narcotized Rats (*M*±*m*, *n*=8)

Drug, dose	Initial values	Shift, %			
		min 5-15	min 30	min 45	min 60
Control	121.5±8.5	0	-0.9±0.9	-1.2±1.3	-2.0±1.2
Bradysole, 0.5 mg/kg	117.3±10.8	-4.5±2.4	-5.2±1.7	-4.2±1.4	-5.6±1.0*
Bradysole, 1.0 mg/kg	113.1±4.7	-6.4±2.2*	-6.9±1.4*	-7.5±2.2*	-9.6±3.1*
Dibasole, 1.0 mg/kg	115.9±3.2	-11.2±3.5*	-20.4±7.6*	-24.4±9.3*	-20.5±7.6*

crease in SBP was a result of the depriming effect of bradysole on heart rate [7], rather than on the peripheral vascular tone. The effect of bradysole on SBP manifested directly after its injection, while the effect on CB was delayed and manifested after an appreciable latent period (30 min). This can be explained by high molecular weight of bradysole, responsible for poor passage of this compound through the blood-brain barrier. The presence of delayed moderate effect on CB could be due to the effects of active bradysole metabolites penetrating through the blood-brain barrier [7].

Dibasole injection in a dose of 1 mg/kg resulted in an increase of CB as soon as for min 5 by 12.7%. With time the drug effect increased, reaching the peak by min 45 (increase of CB by 25.7%). SBP decreased from 11.2% (min 5-15) to 24.4% by min 45 under the effect of dibasole. The effects of dibasole on CB and SBP decreased by min 60, though the shifts in the parameters remained statistically significant (21.8% increase of CB and 20.5% decrease of SBP).

Hence, though bradysole and dibasole caused similar changes in the studied parameters (CB increase and SBP decrease), the effect of bradysole (1 mg/kg) was less pronounced in comparison with its structural analog dibasole (1 mg/kg).

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