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Cardiovascular Properties of New Imidazolidin-2-one Derivatives with Local Anesthetic and Antiarrhythmic Activity

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Abstract

A series of the new imidazolidyn-2-one derivatives with local anesthetic and a slight antiarrhythmic properties was tested for antihypertensive, electrocardiographic and cardiodepressive activity. All of these compounds had a two-stage effect on the arterial blood pressure, an earlier hypotensive phase occurring in the minutes immediately after *i.v.* administration and a later hypertensive phase, maintained at 28.6% for at least two hours observation. Some of the compounds of this series showed a cardiodepressive activity.

Key words :imidazolidin-2one derivatives, cardiovascular activity

Introduction

Recently, we reported [Librowski *et a.l.* 2000] the local anesthetic and antiarrhythmic properties of some imidazolidin-2-one derivatives. In continuation of our study, we now report their influence on the arterial blood pressure and respiration, on the electrocardiogram and on the isolated rat heart. The chemical structure of tested compounds is presented in Table 1.

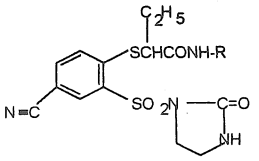
Experimental

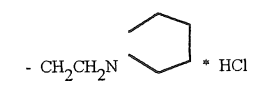
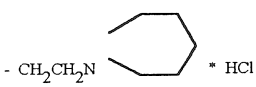
Materials

Animals: The studies were carried out on male Wistar rats (weight 140-250 g). Animals were housed in wire mesh cages in a room at 20 $\pm 2^0$C with natural light-dark cycles. The animals had free access to standard pellet diet and water and used after a minimum of 3 days acclimation to the housing conditions. Control and experimental group consisted of 8-10 animals each.

Doses and route of administration: The investigated compounds were administered intravenously (*i.v.*) as solution in 0.9% NaCl, in doses corresponding to 1/20, 1/10/ 1/5 and 2/5 LD_{50} in constant volume of 1 ml/kg.

Table 1.Chemical structure of investigated compounds



R	Symbol	Compound	LD_{50} [mg/kg]
- $CHCH_2N(CH_3)_2$ * HCl | CH_3	BF-17	(1-{5-cyano-2[1-(1-dimethylamino-2-propylcarbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one hydrochloride)	74 (71.0 - 77.1)
- $CH_2CH_2N(CH_3)_2$ * HCl	BF-18	(1-{5-cyano-2[1-(2-dimethylamino-ethyl-carbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one hydrochloride)	58 (55.9 - 60.1)
	BF-19	(1-{5-cyano-2[1-(2-pirolidin(e)-ethyl-carbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one hydrochloride)	50 (46.2 - 54.0)
	BF-20	(1-{5-cyano-2[1-(2-piperidine-ethyl-carbamoyl)-propyl-thio]-benzene(e) sulphonyl}-imidazolidyn-2-one hydrochloride)	57 (54.0 - 60.1)

Compounds used: Pentotal (Thiopentone sodium, Abbott Laboratories), phentolamine (Regitine *in subst.*, Ciba), reserpine (Raupasil, Polfa).

Statistical analysis. The data are expressed as means ± SEM. Student's t-test was used to determine the significance between mean values of control and treatment groups. Differences were considered significant when $p < 0.05$.

Methods

1.The influence on the blood pressure and respiration

Measurements were carried out on normotensive rats. The animals were anesthetised with intraperitoneal pentotal administration at a 75 mg/kg dosage. Blood pressures were recorded in the left common carotid artery using an electromanometer of type EK-4 together with a recorder WTR-331. The compounds examined were administered to rats

tail vein as solids at 37-38°C in a range of dosage 1/20-2/5 LD_{50}. Simultaneous blood pressure measurements and changes in respiration were recorded.

2.The influence on rats' blood pressure after phentolamine and reserpine pharmacology premedications

Examinations were carried out on normotensive rats anesthetised with pentotal at a regime: 75 mg/kg dosage i.p., followed by intravenous regitine in a dose of 1 mg/kg. The compounds examined were given 15 min. later. The adrenergic blockade (alfa-receptor) was controlled by intravenous administration of adrenaline at a 20 μg/kg dosage. A similar experiment was carried out on rats, which were given reserpine at a 5 mg/kg i.p., 24 hours before the test.

3.Effect on the electrocardiogram

Electrocardiographic studies were carried out on anesthetised rats using a Multicard E-30 apparatus. ECG was recorded from the second extremity lead at a tape feed of 50 mm/s. The influence of the compounds studied on the frequency of myocardiac contraction, the P wave and QRS syndrom were determined.

4.Effect on the isolated rat heart acc. to Langendorff [Langendorff, O. 1895].

Varying dosages of compounds (in μg) and control solutions were hypervalve injected in increments of 0.1 ml. The frequency, amplitude, and coronary influence were determined (recorder TZ-4100).

Results

1. The influence on the blood pressure and respiration

The character of the action of the compounds studied (Serie BF) and their effective intravenous dosages are reported in Table 2.

Two phases of actions were found: an early phase in the first minutes after the intravenous administration (1/20, 1/10, 1/5 and 2/5 LD_{50}) and a late phase occurring after 15 minutes. In the first phase there was a constant hypotension whereas in the second phase an increasing hypertension always occurred. The strongest hypertension effects were showed by compounds BF-18 and BF-19. When administered in the highest dosages (2/5 LD_{50}) they increased the arterial blood pressure in the first two hours of observations by about and 28.6%. Although immediately after intravenous administrations the imidazolidin-2-one derivatives (1/5-2/5 LD_{50}) weakly activated the respiration, they did not have a significant influence on either the amplitude or frequency of respiratory movements.

2.The influence on rats' blood pressure after phentolamine and reserpine pharmacology premedications

The earlier blockage of the sympathetic system in rats by phentolamine intravenous administration in 1 mg/kg dosage, reversed the late hypertension phase, a characteristic of compounds of the BF series. An earlier peripheral sympatholysis, produced by intraperitoneal administration of reserpine, at a dose 5 mg/kg, entirely annulled the hypertension reaction of BF-17 and BF-18 (2/5 LD_{50}).

Table 2. Changes in the blood pressure, expressed as a percentage of the decrease or increase of the BF compounds.

Animal: rat, weight 140-220 g

Compound	Dose x/LD_{50} I.V.	Blood pressure (mm Hg)				
		Starting blood pressure	Time of measuring blood pressure after administration (min.)			
			1	15	30	60
BF-17	1/20	135.0 (105 - 140)	132.0 ↓2.2.0	135.0 0	132.5 ↓2.0	
	1/10	127.0 (110 - 130)	115 ↓9.8	132.5 ↑3.9	135.0 ↑5.9	
	1/5	122.5 (95 - 125)	112.5 ↓8.2	128.7 ↑5.1	138.7 ↑13.2	
	2/5	123.3 (95 - 125)	100.0 ↓18.9	125.8 ↑2.0	134.2* ↑8.8	137.5* ↑12.0
BF-18	1/20	120.0 (100 - 130)	85.0 ↓29.2	110.0 ↓8.3	107.0 ↓10.4	
	1/10	105.0 (105 - 125)	90.0 ↓14.3	110.0 ↑4.8	115.0 ↑9.5	
	1/5	116.6 (95 - 125)	100.0 ↓14.3	125.0 ↑7.2	135.8 ↑16.5	
	2/5	118.3 (105 - 125)	103.3 ↓12.7	125.0 ↑5.6	136.6* ↑15.2	135.0* ↑28.6
BF-19	1/20	120.0 (100 - 130)	100.0 ↓16.7	120.0 0.0	120.0 0	
	1/10	110.0 (95 - 130)	102.5 ↓6.9	110.0 0	107.5 ↓2.3	
	1/5	125.0 (95 - 130)	110.0 ↓12.0	135.0 ↑8.0	145.0 ↑16.0	
	2/5	116.6 (95 - 125)	105.0 ↓10.0	118.3 ↑1.4	128.3* ↑10.0	120.0* ↑14.3
BF-20	1/20	125.0 (95 - 130)	117.5 ↓ 6.0	127.4 ↑2.0	127.5 ↑2.0	
	1/10	125.0 (95 - 130)	110.0 ↓ 12.0	125.0 0	125.0 0	
	1/5	121.7 (105 - 125)	111.7 ↓ 8.2	125.0 ↑2.7	130.0 ↑6.8	
	2/5	116.2 (95 - 125)	93.7* ↓19.4	121.2 ↑4.3	132.5* ↑14.0	132.5* ↑10.4

%↑ Increase; %↓decrease* $p < 0,05$.

3. The effect on the electrocardiogram

In the electrocardiographic rat curve, just as in human, we may distinguish P, Q, R, S and T waves. The base rhythm is sinusoidal, regular with a frequency in the range 333-429 contractions per minute, most frequently, about 375 contractions per minute. No fluctuation of the velocity of the heart action in the same rat during a single examination is observed. There is no correlation between the heart action velocity and the body mass of the animal.

The compounds (BF-17, BF-18, BF-19 and BF-20) given i.v. at doses corresponding to 1/20 - 2/5 LD_{50} have no effect on the rat heart electrocardiogram. At these doses any significant changes in the ECG curve course through the 1.5 hours of observation would have been noted. At doses of 2/5 LD_{50} , however they significantly slacken the working heart frequency causing bradycardia. The strongest action occur after administration of BF-17 and BF-19 (22.7% and 22.4%).

4. The effect on the isolated rat heart acc. to Langendorff

The compounds studied have an effect on the systolic-diastolic amplitude, frequency of contraction and the flow through the coronary vessels (Table 3).

Table 3. Effect on the isolated rat heart of BF compounds

Compound	Dose µg	Per cent of decrease		
		Frequency	Amplitude	Coronary outflow
BF-17	2000	29.6	79.9	30.5
BF-18	100	10.3	↑5.6	14.7
	200	14.7	9.2	36.1
	2000	20.7	53.2	52.1
BF-19	2000	9.1	↑25	18.3
BF-20	50	0	↑6.2	2.4
	100	1.7	↑17.4	5.2
	2000	11.9	↑22.2	17.9

Animal: Wistar rats, weight 140 - 220 g, N = 8 – 10; ↑ Increase

Compound BF-17 in a doses of 10 - 1000 µg did not influence on the isolated heart. In a dose of 2000 µg reduced the systolic-diastolic amplitude by 79.9%, the frequency of contraction by 29.6%, the flow through the coronary vessels to about 30.5%.

Compound BF-18 in a doses of 100 - 2000 µg reduced the coronation frequency by about 10.3-20.7%, the coronary blood flow by about 14.7 - 52.1%. The heart amplitude was at first slightly higher (100 µg) and next decreased by about 9.2-53.2% (200-2000 µg).

Compound BF-19 in a dose of 2000 μg slacken the frequency of myocardial contractions by about 9.1% and decreased the coronary blood flow by 18.3%. The heart amplitude increased by 25%.

Compound BF-20 in a doses of 10 - 2000 μg did not influence on the isolated heart. After 10 - 20 μg doses a significant influence on coronary blood flow was observed; higher doses of 50 -2000 μg decreased the coronary outflow by about 2.4-17.9%. Doses of 20 μg and 50 μg had no influenced on the frequency of contractions but higher doses (ca. 100 - 2000 μg) decreased the frequency of contractions by about 1.7 -11.9%. The heart amplitude increases according to the dose: 50 μg by about 6.2%, 100-2000μg by about 17.4 - 22.2%.

Discussion

Contemporary medicine has available many antiarrhythmic drugs. Unfortunately various studies have demonstrated that all these drugs possess side effects (torsade de pointes, AV block, negative inotropic and chronotropic effects, hypotension, bradycardia, heart failure), [Hoffmeister, H.M. *et al.* 1997, Lazzara, R. 1996, Nolan, P.E. 1997, Pratt, C.M. *et al.* 1998, Reiffel, J.A. *et al.* 1997, Singh, B.N. 1996, Singh, B.N. 1997, Singh, B.N. 1997]. Hence trials of newly synthesised chemicals of expected antiarrhythmic activity are continually undertaken [Filipek, B. *et al.* 1997, Leite, L. *et al.* 1999, Librowski, T. *et al.* 1998, Librowski, T. *et al.* 2000, Pascal, J-C. *et al.* 1990, Uchida, Y. *et al.* 1998]. In an attempt to discover a new antiarrhythmic drug with a better safety and efficacy profile, a series of the four new derivatives of imidazolidin-2-one with local anesthetic and antiarrhythmic activity was investigated in order to determine their influence on the cardiovascular system.

Our results, obtained in normotensive anesthetized rats, show that investigated compounds have a two-stage effect on the arterial blood pressure, an earlier hypotensive phase occurring in the minutes immediately after *i.v.* administration and a later hypertensive phase, maintained for at least two hours observation. In the dosages used, the compounds have no influence on either on either the amplitude nor frequency of respiration. Pretreatment with phentolamine or reserpine did not change or only slightly decreased the hypotensive effect of tested compounds, but antagonised their hypertensive effect. These results suggest that the hypertensive response which was observed after the new imidazalidin-2-one derivatives is probably called out enlargement of releasing endogenic catecholamine.

In the range 1/10-2/5 LD_{50} no influence on ECG measurement parameters were observed although they caused bradycardia. Moreover the imidazolidin-2-one derivatives showed a cardiodepressive activity – a reduction of coronary outflow and contraction frequency of the isolated rat's heart. Obtained results show, that the all investigated compounds possess adverse events, what at their weak antiarrhythmic activity excludes it from further pharmacological screening.

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