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LOCAL ANESTHETIC AND ANTIARRHYTHMIC EFFECT OF SOME IMIDAZOLIDIN–2–ONE DERIVATIVES

TADEUSZ LIBROWSKI, BARBARA FILIPEK and RYSZARD CZARNECKI

Department of Pharmacodynamics, Collegium Medicum Jagiellonian University, 9 Medyczna Str., 30–688 Kraków, Poland

Abstract: A series of the new derivatives of imidazolidin–2–one was investigated in order to determine their local anesthetic and antiarrhythmic activity. All compounds tested showed strong local anesthetic properties and variable effects on adrenaline–, aconitine– and barium chloride– induced arrhythmia. The results suggest that the antiarrhythmic properties of these compounds is related to their local anesthetic properties.

Keywords: Imidazolidin–2–one derivatives – local anesthetics – antiarrhythmic activity.

The local anesthetic effect is characteristic for the antiarrhythmic drugs of I class, i.e. drugs which stabilize the cellular membranes and modulate sodium channel activity (2, 3, 14, 15). Numerous earlier studies suggested correlation between sodium–channel antagonists of this class and its antiarrhythmic activity (3, 4, 11).

The subject of this study was anesthetic effect and antiarrhythmic effect of new imidazolidin–2–one derivatives, which were synthesized in the Department of Chemical Technology of drugs in the Faculty of Pharmacy of the Medical Academy in Gdańsk (Table 1).

MATERIALS AND METHODS

Compounds used

Epinephrine (Adrenalinum hydrochloricum Polfa), aconitine (Aconitinum nitricum in subst., Toscat), barium chloride (POCh Gliwice), lidocaine (Lignocainum hydrochloricum, Polfa), pentotal (Thiopental sodium B.P., Abbott Laboratories), propranolol (Propranololum hydrochloricum, Polfa), quinidine sulfate (Polfa).

Animals

The studies were carried out on male Albino Swiss (weight 18–24 g), male Wistar rats (weigt 140–220 g) and guinea pigs of both sexes (weight 300–350 g). Animals were housed in wire mesh cages in a room at 20 ± 2°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 routes of administration

Depending on the experimental method, the tested compounds were given intravenously, in doses corresponding to 1/20, 1/10, 1/5 and 2/5 LD_{50} or intradermally and topically, in the form of 0,5, 1 and 2% stolutions.

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 $p<0.05$.

EC_{50} values and their confidence limits were calculated according to the method of Litchfield and Wilcoxon after 30 min observation.

I. Local anesthetic activity acc. to Bülbring and Wajda (1)

A. Corneal anesthesia

The compounds studied were instilled to the right conjunctival sac as a 0,5; 1,0 and 2,0% solutions in the same volume 0,05 ml, on the contrary to the left eye the same volume of 0,9% NaCl.

The corneal reflex was examined by irritation a right eye conjunctiva (studied eye) and a left eye conjunctiva (control eye) by horse's hair. The strength of local anesthetic activity was determined from the moment of solution instillation to the moment of reflex return. The presence or lack of corneal reflex were considered during an activity assessment. The eye conjunctiva irritation was done 6 times (every 5 sec) in the pause of 5 minutes during the first 30 minutes. The sum of the ir-

ritation, for what guinea pig did not react to each of the above concentrations (in %) served to assess EC_{50}.

B. The infiltration anesthesia (intradermal wheal test)

The infiltration anesthesia was done on guinea pig, causing the intradermal wheal by injection to the dorsum skin compounds studied in volume 0,1 ml and dosages 0,5; 1,0 or 2,0%.

The painful reaction to prick was registered pricking 3 times the skin at the center of the wheal (every 5 sec) in 5 minutes intervals during the first 30 minutes of observation and next after 15 minutes. Experiment was continued to achieve the return of reaction for a prick.

The control wheal was done by an intradermal injection of 0,1 ml 0,9% NaCl. The comparable studied of duration time of infiltration anèsthesia in guinea pigs were done using lidocaine in dosage 0,1; 0,5 and 1,0%. The differences between control and studied groups were estimated by EC_{50}.

II. Prophylactic antiarrhythmic activity

A. Adrenaline–induced arrhythmia acc. to Szekeres (13)

The arrhythmia was evoked in rats anesthetized with thiopental (75 mg/kg, *ip*) by intravenous injection of adrenaline (20 μg/kg, in volume of 1 ml/kg animal weight). The studied compounds were administered intravenously 15 min before adrenaline. Evaluation of the antiarrhytmic activity was made acc. to the time of occurring postadrenaline disorders and the survival time of animals in control and studied group. ECG was recorded on a Multicar E–3 or E–30 apparatus, using the standard limb lead, and the tape speed 50 mm/s.

B. Aconitine–induced arrhythmia acc. to Szekeres (13)

The arrhythmia was evoked in rats anesthetized with thiopental (75 mg/kg *ip*) by *iv* injection of aconitine (10 μg/kg). The investigated compound was given *iv* 15 minutes before the arrhythmogen (prophylactic activity). The time of onset of severe ventricular arrhythmia's or the time restoration of the sinus rhythm and mortality in a particular group were accepted as a criterion of evaluation.

C. Barium chloride–induced arrhythmia acc. to Szekeres (13)

Barium chloride solution was injected into the caudal vein of rat (32 mg/kg, in a volume of 1 ml/kg). The investigated compound was given *iv* 15 minutes before the arrhythmogen. The criterion of antiarrhytmic activity was a gradual disappearance of the arrhythmia and restoration of the sinus rhythm.

III. Acute toxicity acc. to Litchfield and Wilcoxon (6)

Acute toxicity was assessed according by the method of Litchfield and Wilcoxon and presented as LD_{50} calculated from the mortality of mice after 24 hours.

RESULTS

I. Local anesthetic effect

A. Corneal anesthesia

The new derivatives of imidazolidin–2–one applied into the conjunctival sac in a concentration of 0,5; 1,0 and 2,0% did not exert local anesthetic activity.

B. Infiltration anesthesia

Compound BF–17, BF–18, BF–19 and BF–20, injected intradermally at concentrations of 0,5–2%, showed strong anaesthetic effect. The strongest effect, higher than that lidocaine, was shown by compound BF–19 and BF–20. Compounds BF–17 and BF–18 produced an effect similar to that of lidocaine. The duration time of anesthesia after tested compound was 2–4 h and was considerably longer than that of lidocaine (40–50 min). Administration of compound BF–21 and BF–22 was impossible to cause a low solubility of this compounds. The EC_{50} values determined after 30 min observation period are presented in Table 2. The data reported in Table 2 indicate that the therapeutic index of investigated compounds was more favorable than for lidocaine.

Prophylactic antiarrhythmic activity

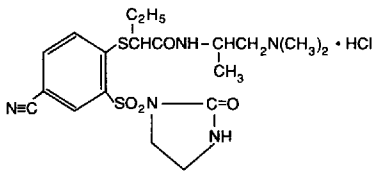
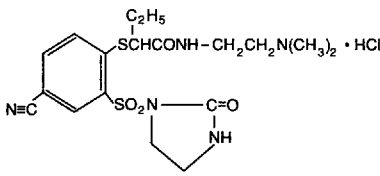
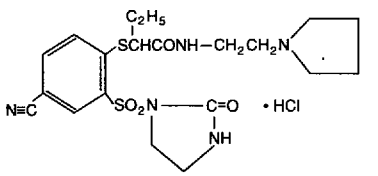
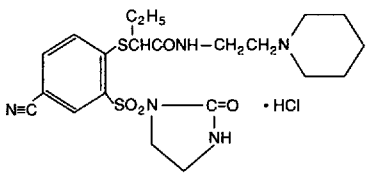
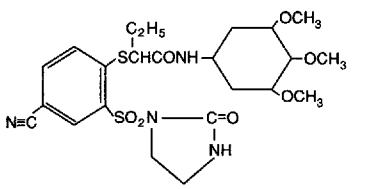
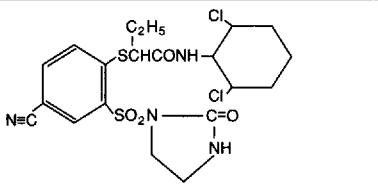
A. Adrenaline–induced arrhythmia

The intravenous injection of adrenaline, in the dose of 20 μg/kg, caused ventricular tachycardia and supraventricular ectopic beats. All new compounds administered *iv* 15 min before adrenaline in doses of 1/10 to 2/5 LD_{50}, contrary to propranolol (ED_{50}–1,05 (0,64–0,73) did not prevent adrenaline–induced disturbances. Only compound BF–17 and BF–18 given in highest dose showed lowest antiadrenaline activity (Figure 1).

B. Aconitine–induced arrhythmia

Aconitine (10 μg/kg *iv*) caused in rats at-

Table 1. Acute toxicity (Litchfield, Wilcoxon). Time: 24 h, Route: *iv*, Animal: mouse

Structural	Symbol	Compound	LD_{50}[mg/kg]
	BF-17	1-{5-cyano-2[1-(1-dimethylamino-2-propylcarbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one hydrochloride	74 (71.0-77.1)
	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 sulphonyl}-imidazolidyn-2-one hydrochloride	57 (54.0-60.1)
	BF-21	1-{5-cyano-2[1-(3,4,5-trimethoxyphenyl-carbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one	
	BF-22	1-{5-cyano-2[1-(2,6-dichlorophenyl-carbamoyl)-propyl-thio]-benzene sulphonyl}-imidazolidyn-2-one	

rioventricular conduction disorders, ventricular tachycardia and ventricular fibrillation, ending very often by deaths of animals after 12–15 minutes.

The study results of influence of investigated compounds on arrhythmogenic effects caused by intravenously administered aconitine were showed in Table 3. The antiarrhythmic activity of BF compounds was evaluated on the basis of time delay of arrhythmia appearance and extension of animal time survival. All the compounds studied, to be sure, exerted the prevention influence on animals mortality, caused by aconitine intravenously administered, made however in the high dosage equal to 2/5 LD_{50}.

The BF series compounds in the dosage 2/5 LD_{50} intravenously administered 15 minutes before aconitine injection caused appearance delay of the arrhythmia with very mean decrease of the ventricular heterotropy. The relative high activity strength distinguished the BF–19 compound. The intravenous dosages of this compound in 2/5 LD_{50}, administered 15 minutes before the aconitine injection, led to delay of the disorders of the rhythm from 60 sec in control to 390 sec the groups studied.

Therefore the BF–19 compound delayed at 550% appearance period of the aconitine arrhythmia and protected also before appearance of toxic

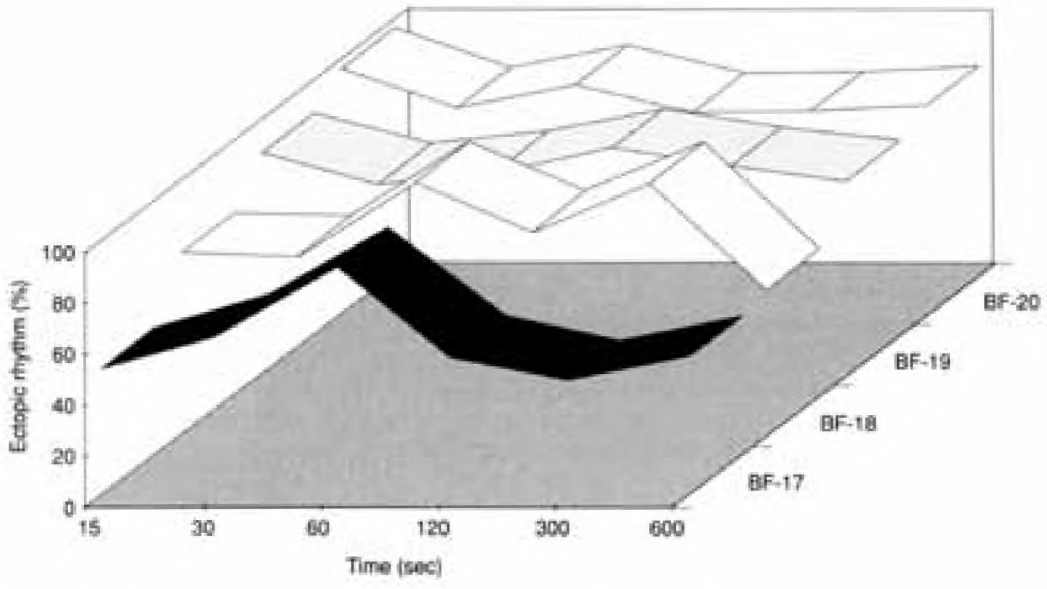


Figure 1. Antiarrhythmic activity of the investigated compounds on the adrenaline-induced arrhythmia.
Animal: rat, weight 140 -220 g, N = 8 - 10
Arrhythmogen: adrenaline, 20 µg/kg i.v.
Compounds: *iv* 15 min before the arrhythmogen

Table 2. Local anesthetic activity of investigated compounds

Compound	Concentration (%)	Activity (%)	EC_{50} (%)	TI (LD_{50}/EC_{50})
Lidocaine	0.1 0.5 1.0	39.0 59.3 87.0	0.36 (0.18-0.74)	83.33
BF-17	0.5 1.0 2.0	50.0 67.6 89.4	0.52 (0.28-0.92)	142.31
BF-18	0.5 1.0 2.0	71.3 80.8 96.7	0.31 (0.15-0.69)	187.09
BF-19	0.5 1.0 2.0	76.9 73.2 89.1	0.105 (0.098-0.210)	476.19
BF-20	0.5 1.0 2.0	82.5 85.5 87.9	0.101 (0.086-0.198)	564.45

Results are expressed as a mean ±SEM; N=8-10.
The EC_{50} values are given with 5% confidence limits.

phase – extended the animal survival times. The animal morality yielded prolongation (BF–19) about 26% to compare with the control group getting only alone aconitine.

BF–17 compound similar antiarrhythmic and antitoxic activites showed. BF–17 administered intravenously in the dosage of 2/5 LD_{50} before aconitine injection delayed at about five times

Table 3. Antiarrhythmic activity of the investigated compounds in aconitine-induced arrhythmia.
Animal: Wistar rates, weight 140–220 g
Arrythmogen: aconitine, 10 μg/kg i.v.
Compounds: i.v. 15 min before the arrhythmogen

Compound	Dose mg/kg *iv* 2/5 LD_{50}	Appearance time of arrhythmia (sec)	Prolongation time of arrhythmia (%)	Mortality after (sec)	Survival time extension (%)
Control	0	60 ± 11.8	-	828 ± 115	-
BF–17	29.6	336 ± 82.7	460 ± 23.15	1380 ± 245	66.67 ± 5.65
BF–18	23.2	120 ± 34.8	100 ± 15.59	1260 ± 180	52.17 ± 0.71
BF–19	20.0	390 ± 87.4	550 ± 18.62	1044 ± 128	26.08 ± 1.1.79
BF–20	22.8	210 ± 69.7	250 ± 39.55	1008 ± 125	21.17 ± 1.02
Quinidine	30.0	130 ± 39.6	117 ± 19.21	1280 ± 195	54.59 ± 1.82

Results are expressed as a mean ± SEM; N=8-10

arrhytmia appearance and extended the animal survival times by about 67%. The observed effect was stronger than that of quinidine.

The other investigated compounds (BF–18, BF–20) showed the considerable weaker activities, but the antiarrhythmic effect of BF–18 and BF–20 was comparable to that reported for quinidine in the same procedures (Table 3).

C. Barium chloride–induced arrhythmia

A single *iv* dose of 32 mg/kg $BaCl_2$ induced progressively increasing disturbances of cardiac rhythm, associated with premature ventricular beats and ventricula fibrillation, leading to death within 20–25 min.

The compounds studied (BF–17–20), given in the dose of $2/5LD_{50}$ did not prevent the occurrence of heart rhythm disorders caused by barium chloride. They also did not prevent before occurrence of the toxic phase as mortality caused by barium chloride. Only BF–19 and BF–20 extended the animals survival times adequate to 2 and 6 times in comparison to the control group.

III. Acute toxicity

Compounds BF–17–20, applied intravenously were less toxic than lidocaine (LD_{50} = 25,0–27,5). Compound BF–21 and BF–22, as insoluble in water, were exclude in this study. The values of *iv* LD_{50} in mice are reported in Table 1.

DISCUSSION

At present four major classes are available for the management of cardiac arrhythmia: local anesthetics (class I), beta–blockers (class II), class III antiarrhythmic agents (i.e. prolongation of repolaryzation), and the calcium–channel antagonists (class IV). Class I antiarrhythmic drugs block the fast sodium channel and possess local anesthetic activity (2, 9, 15).

A number of earlier studies suggested some association between local anesthetic and antiarrhythmic activity (3, 4, 10, 11). It was concluded that local anesthetic activity is not a necessary concomitant to antiarrhythmic activity and that local anesthetic activity might be more correctly associated with depression of cardiac conduction and contractility (8, 11).

Previous pharmacological screening for new cardiovascular agents led to discovery of antiarrhythmic and local anesthetic activity of (–)–trans–4–[2–hydroxy–3–(N–isopropyloamino)–proxy]–cic carane (5, 12). As a continuation of our study, we demonstrated the local anesthetic and antiarrhythmic activity of some imidazolidin–2–one derivatives.

The obtained results indicate that the investigated new imidazolidyn–2–one derivatives demonstrated potent local anesthetic properties when applied intradermally to the conscious guinea pig. The effect was stronger than that of lidocaine. The therapeutic index of compound BF–19 (1–{5–cyano–2[1–(2–pirolidine–ethyl–carbamoyl)–propyl–thio]–benzene–sulphonyl}–imidazolidyn–2–one hydrochloride) was about six times, and BF–20 ((1–{5–cyano–2[1[(2–piperidine–ethyl–carbamoyl)–propyl–thio]–benzene–sulphonyl}–imidazolidyn–2–one hydrochloride) seven times advantageously that lidocaine.

Two of them, compound BF–17 (1–{5–cyano–2[1–(1–dimethylamino–2–propyl–carbamoyl)–propyl–thio]–benzene–sulphonyl}–imidazolidyn–2–one hydrochloride) and BF–18 (1–{5–cyano–2[1–(2–dimethylamino–ethyl–carbamoyl)–propyl–thio]–benzene–sulphonyl}–imidazolidyn–2–one hydrochloride) given before adrenaline partially prevented the rhythm disturbances. The observed effect was weaker than that of propranolol, which was highly effective in abolishing arrhythmia provoked by the injection of adrenaline (7).

All investigated compounds delayed the occurrence of disturbances produced by the intravenous injection of aconitine in rats and prolonged the animal survival time. The observed antiarrhythmic effect was similar or stronger that the effect of quinidine.

In comparison with control group, tested compounds, did not prevent barium–chloride induced heart dysrrhythmias, but compounds BF–19 and 20 prolonged two–fold and six–fold the animals survival time.

In summary, investigated new imidazolidyn–2–one derivatives demonstrated potent local anesthetic properties and variable effects on adrenaline–, aconitine–, and barium chloride – induced arrhythmia. The antiarrhythmic properties of these compounds in different models of arrhythmia probably are related to their local anesthetic properties, but precise mechanism of action of those drugs to be further studied.

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