Efficacy of Newly Synthesized 44Bu Ultrashort-Acting Beta-Adrenergic Antagonist to Isoprenaline-Induced Tachycardia – Comparison With Esmolol

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Abstract

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The aim of this study was *in vivo* testing of the action of three newly synthesized potential ultrashort acting beta-blockers on the heart rate in the laboratory rat. The tested substance 44Bu was administered to animals with induced tachycardia, in the form of an intravenous bolus in general anaesthesia.

Doses at concentrations of 1.5 $mg \cdot kg^{-1}$, 2.5 $mg \cdot kg^{-1}$, and 3.5 $mg \cdot kg^{-1}$ of body mass were tested and the efficacy was compared with placebo. For the heart rate monitoring a computer electrocardiograph was used. Significant ($p < 0.05$) heart rate decrease was recorded for all three tested doses, minimally up to the 14th minute following the intravenous administration.

Bradycardic effect of the compound 44Bu was compared with the action of esmolol under the same experimental conditions. The effects of the compound 44Bu and esmolol were not different in the onset, but in the depth of the heart rate decrease, above all at higher concentrations. It was experimentally verified, that the compound 44Bu has the properties of an ultrashort acting beta adrenergic receptor blocker.

Pharmacology, ester-functional group, bradycardic effect, heart rate, rats

The beta-adrenergic receptor blockers were introduced in the clinical practice in the early 1960s after their effect on blood pressure reduction had been demonstrated. They are widely used in angina pectoris treatment, and since early 1970s, they are evidenced to reduce mortality after myocardial infarction. Nowadays, the most important indications include ischaemic heart disease, arrhythmias, arterial hypertension. Recently they have been used also in certain types of heart failure (Felix et al. 2001), e.g. idiopathic dilatation cardiomyopathy (Hradec et al. 2002). In addition to these basic indications, they are also used in non-cardiologic diseases treatment, such as glaucoma, migraine, hyperthyroidism or anxiety states. Some representatives of the beta-blockers show also a distinct anti-oxidant effect (Bartošíková et al. 1998; Nečas et al. 1997).

However, the beta-blockers possess also a number of adverse effects, such as bradycardia, hypotension, heart failure and bronchospasm, peripheral vasoconstriction (cold extremities syndrome), fatigue, insomnia, depression.

To avoid prolonged action of beta-blockers, ultrashort acting beta-blockers have been developed for intravenous infusion with several minutes of duration of the pharmacological effect, the use of which is much more convenient than the administration of longer acting beta-adrenergic antagonists in critically ill patients (Reilly et al. 1985; Gray 1988).

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Table 1
Average heart rate values following the administration of 44Bu ± SD and statistical significance

Time interval	Average HR value for placebo	Average HR value after administration of 44Bu								
		1.5mg/kg	Statistics		2.5mg/kg	Statistics		3.5mg/kg	Statistics	
Initial HR	327	287	N t t	P t t	292	N t t	P t t	303	N t t	P t t
HR after ISO	453	457			466			458		
i.v. administration	440	425	*	++	436	*	++	450	*	+
30th second	431	410	**	++	423	**	++	450	**	++
1st minute	443	400	**	++	425	*	++	443	*	++
2nd minute	450	395	*	++	409	**	++	431	*	++
3rd minute	447	392	*	++	412	**	++	439		++
4th minute	457	398	**	++	417	**	++	439	*	++
5th minute	457	403	**	++	423	**	++	439	*	++
6th minute	463	397	**	++	425	**	++	439	**	++
8th minute	467	407	**	++	423	*	++	431	**	++
10th minute	450	403	**	++	420	*	++	434	*	++
12th minute	463	405	**	++	425	*	++	434		++
14th minute	473	408	*	++	417	*	++	436		++
16th minute	467	418	*	++	428		+	425	*	++
18th minute	470	408	**	++	425		+	435	*	++
20th minute	473	407	*	++	431			431	*	++
25th minute	465	407	*	++	417			417		++

N t t = unpaired Student's *t*-test P t t = paired Student's *t*-test
The result of unpaired t-test (determination of the statistical significance of each value as compared to placebo) is marked by asterisk.
$p < 0.01$ ** $p < 0.05$ *
The result of paired t-test (determination of the statistical significance as compared to the initial value) is marked by cross.
$p < 0.01$ ++ $p < 0.05$ +

These compounds have a very short elimination half-time, about 10 minutes (Katzung et al. 1995). Steady concentration is achieved by continuous infusion, and the therapeutic effect can be quickly finished by interrupting the infusion.

The ultrashort acting beta-blockers form so far an inconspicuous fraction of the extensive group of beta-adrenolytics. Currently, three ultrashort acting beta-blockers have been synthesized: esmolol (Gorczynski 1985), flestolol (Barton et al. 1986), and landiolol (Atarashi et al. 2000). Their common feature is a short biological elimination half-time, which is achieved by the ester group integration in the side chain on the aromatic nucleus. This group is hydrolyzed rapidly by cholinesterases in plasma or esterases in cytosol or erythrocyte membrane.

In the Czech Republic, the only registered preparation containing ultrashort acting beta-blocker esmolol is Breviblоc®, inj. The effective substance is esmolol hydrochloride (AISLP 2002). Landiolol was introduced to the market under the name of Onoact®, 50 inj. in Japan last year. The effective substance is landiolol hydrochloride.

The administration of the ultrashort beta-blockers has been increasing continuously, both in emergency situations, when a quick heart rate control is necessary, e. g. in sinus tachycardia, fibrillation and atrium flutter (Blanski et al. 1988) and in therapy or prophylaxis of tachycardia and hypertension arising as a result of increased sympathetic activity in anaesthesia during an operation or in an after-operation phase, e. g. in laryngoscopy or intubation (Bensky et al. 2000). The ultrashort acting beta-blockers are becoming an important therapeutic group, and, consequently, the effort aiming at the synthesis of new substances bearing of these properties appear of interest.

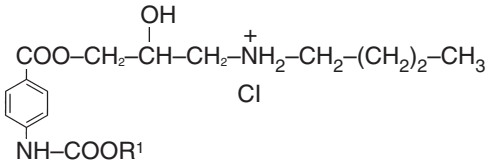
Based on the knowledge resulting from the structure and effect relation, it is possible to presume the beta-blocking effect in compound 44Bu, and regarding the fact that it contains an ester group in p-position on the aromatic nucleus, it is also possible to expect a short period of action due to the short biological elimination half-time. The aim of this study was to find the relation between the compound 44Bu doses and their pharmacological effect.

Materials and Methods

Tested Substance

The tested compound 44 Bu (structure see Fig. 1) was prepared by five-step synthesis, and the structure was verified by elementary analysis, IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy (Mokrý et al. 2001).

2-hydroxy-3-(butylamino) propyl-4-[(butoxycarbonyl) amino] benzoate hydrochloride



R^1	Tt (°C)	Summary formula	Mr	Rf
C_4H_9	10--112	$C_{19}H_{31}N_2O_5CI$	402.92	0.69 CET 4:2:1

Fig. 1. Structure of the tested substance 44Bu

This compound belongs in the category of the newly synthesized compounds with potential beta-blocking effect with ultrashort action. The ultrashort action is achieved by the incorporation of metabolically unstable ester functional group in the linking chain of the aryloxyaminopropanol structure of original beta blockers (Mokrý et al. 2003).

In compound 44Bu similar biotransformation is supposed as in flestolol, which also belongs among the ultrashort acting beta-blockers. The ester group in the linking chain of the compound 44Bu is split by plasma esterases in blood plasma. It is assumed that through the action of carboxyl esterases two metabolites are formed, namely 4-alkoxycarbonyl aminobenzoic acid and 3-alkylaminopropan-1,2-diol.

Experimental Animals

The testing was performed *in vivo* in fifty five male Wistar laboratory rats (body mass of 446 ± 25 g) with normal blood pressure. The animals came from a conventional breeding colony (Faculty of Medicine, Masaryk University, Brno). They were housed in agreement with the conditions as per Regulation No. 311/1997 Coll. (temperature - 20-24 °C, humidity 40-60%, 12:12 h L:D cycles with lighting maximum up to 200 lux. They were placed in PVC cages with three animals each). The animals were fed a standard diet (Diet for small laboratory animals M_1) and given water *ad libitum*.

Methodology of the experiment was approved and monitored by the local University Ethical Committee of VFU under ref. No. 12609/2003-30/300.

Experimental Design

The experiment was arranged as a comparative testing of the dose-dependent compound 44Bu action on heart rate. The measurement was taken in the group of ten rats for each dose.

Control group (n=6) was given 1 ml of saline (placebo) in the same way.

As a comparative compound esmolol (Brevibloc® inj. Baxter Healthcare Ltd., UK) was used. The measurement was carried out in the group of six animals for each dose.

Procedure

The animals were anaesthetised using a 1% solution of ketamine (Narkamon®, inj. Spofa, Czech Republic) and 2% solution of xylazine (Rometar®, inj. Spofa, Czech republic). Saline was used for dilution (sterile isotonic 0.9% NaCl solution for infusion). The anaesthetic agent was administered intramuscularly into the femur area at the dose of 0.5 ml/100 g of body mass.

The heart rate changes were measured on a model of induced tachycardia, which was induced by subcutaneous administration of isoprenaline (Isuprel®, inj. Abbott S.p.A. Campoverde LT - Italy). In the experiment the recommended concentration 4 $mg \cdot kg^{-1}$ of the body mass was used (Český lékopis - Czech Formulary, 1997). The heart rate reached its maximum of 150.37% of the initial value after 8 – 10 min. The induced tachycardia was stable for a minimum of 30 min following the administration. The prepared tested substance was given intravenously into vena jugularis as a bolus dosage at a concentration of 1.5 $mg \cdot kg^{-1}$, 2.5 $mg \cdot kg^{-1}$, and 3.5 $mg \cdot kg^{-1}$of the body mass. The standard volume was 1 ml. The time interval of administration was 20 s.

For monitoring the heart rate the SEIVA EKG Praktik electrocardiograph with appropriate software was used. The ECG records were made in the predetermined time intervals. The first record was taken at the beginning of the experiment after the induction of general anaesthesia, the second 10 minutes after the subcutaneous isoprenaline administration. This value corresponded with the initial value of tachycardia and it was marked as 100 %. Other records were made at the time of intravenous administration, further from the time of administration (marked 0) every thirty seconds up to the first minute, from the 1st up to the 6th minute every one minute, and from the 6th up to the 20th minute in two minutes intervals. The last record was made in the 25th minute. All detected values are given in Figs 2-7.

Statistical Analysis

Statistical computations were carried out in the programs Unistat 5.1 and Microsoft Excel. A standard deviation was calculated for each value.

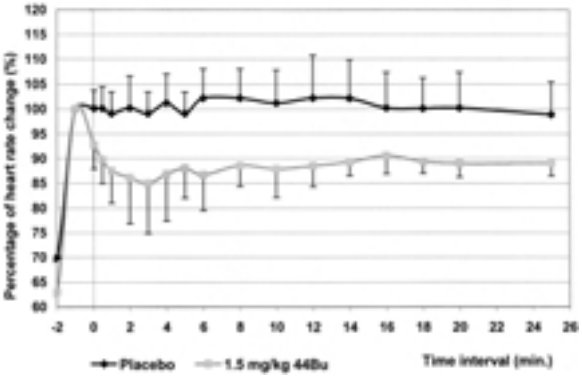
For the comparison of differences between placebo action and that of three different compound 44Bu concentrations (or three different esmolol concentrations) the ANOVA test was used. To reveal the statistically significant differences, Student's *t*-test (paired and unpaired) was used. By means of that, we defined the statistical significance of the observed changes of the tested substance in all three concentrations both against the control group (placebo) and the heart rate changes, which were induced by esmolol at the same concentration (see Table 1 and 2).

Results

The onset of action was very fast for all tested concentrations of 44Bu. We recorded a significant decrease of the heart rate both compared to control group (placebo) and the initial tachycardia value during the time of administration.

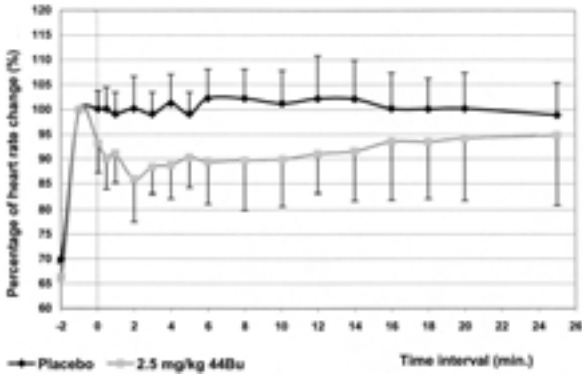
The maximum heart rate decrease of the 44Bu at the dose of 1.5 $mg \cdot kg^{-1}$ equaled 85.36 ± 10.14% of the initial value and it was achieved in the 3nd minute following the intravenous administration (Fig. 2). The concentration increase to 2.5 $mg \cdot kg^{-1}$ led to a heart rate decrease of 85.94 ± 8.43% of the initial value in the 2nd minute following the administration (Fig. 3). Further dose increase to 3.5 $mg \cdot kg^{-1}$ led to a heart rate decrease only to 91.04 ± 9.32% of the initial value (Fig. 4) in the 2nd minute.

The significant heart rate decrease in comparison to placebo lasted minimally up to the 14th minute following the intravenous administration for all three concentrations – at the dose of 1.5 $mg \cdot kg^{-1}$ of



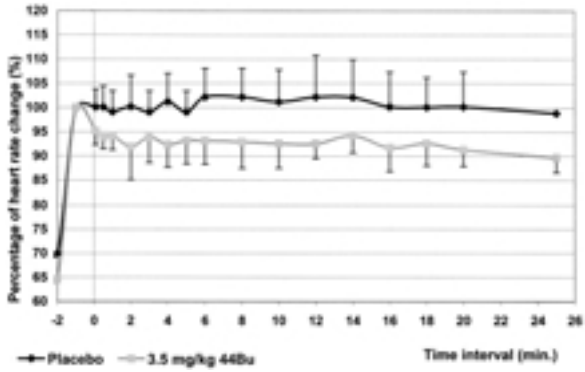
The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 2. Heart rate change (in %) following the administration of 44Bu at the concentration of 1.5 mg·kg^{-1}



The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 3. Heart rate change (in %) following the administration of 44Bu at the concentration of 2.5 mg·kg^{-1}



The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 4. Heart rate change (in %) following the administration of 44Bu at the concentration of 3.5 mg·kg^{-1}

the body mass the heart rate decrease was significant even up to the 25th minute following the intravenous administration (Table 1).

Immediately after the intravenous administration of the compound 44Bu, we recorded very distinct changes in ECG record concerning above all PQ interval, QRS complex, QT interval, and moreover S, R wave and T wave (Bartošová et al. 2003).

Also the onset of action of esmolol was very fast. The statistically significant heart rate decrease in comparison to placebo occurred during the time of administration. The maximum heart rate decrease of esmolol at the dose of 1.5 mg·kg^{-1} equaled 80.94 ± 7.24% of the initial value and it was achieved in the 2nd min following the intravenous administration (Fig. 5). The concentration increase of esmolol to 2.5 mg·kg^{-1} led to a heart rate decrease to 75.6 ± 6.23% of the initial value in the 30th second following the intravenous administration (Fig. 6). Further dose increase of esmolol to 3.5 mg·kg^{-1} led to even more distinct heart rate decrease, the maximum equaled 70.55 ± 2.85% of the initial value and it was reached in the 30th second following the intravenous administration (Fig. 7, Table 2).

Discussion

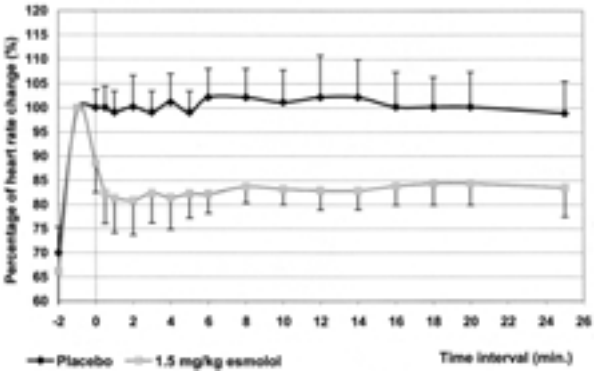
The substance tested with the working name 44Bu belongs to the category of potential drugs with the ultrashort acting beta-blocking action. From the chemical point of view it is a 2-hydroxy-3-(butylamino) propyl-4-[(butoxycarbonyl) amino] benzoate hydrochloride.

All the tested concentrations of the compound 44Bu caused the significant heart rate decrease against placebo (Fig. 2-4). Immediately after the intravenous administration of 44Bu distinct changes in ECG record were observed (for actual results see Brunclík et al. 2003).

Table 2
Average heart rate values following the administration of esmolol ± SD and statistical significance.

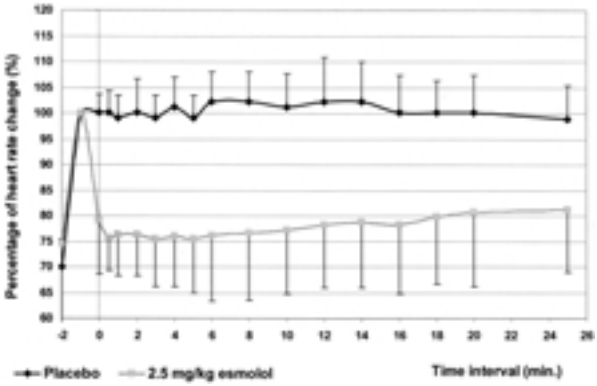
Time interval	Average HR value for placebo	Average HR value after administration of esmolol								
		1.5mg/kg	Statistics		2.5mg/kg	Statistics		3.5mg/kg	Statistics	
Initial HR	327	276	N t t	P t t	288	N t t	P t t	280	N t t	P t t
HR after ISO	453	424			388			434		
i.v. administration	440	374	**	+	304	*	+	348	**	++
30th second	431	348	**	++	292	**	++	308	**	++
1st minute	443	344	**	++	294	**	++	316	**	++
2nd minute	450	342	**	++	294	**	++	326	**	++
3rd minute	447	348	**	++	290	**	+	328	**	++
4th minute	457	344	**	++	292	**	+	330	**	++
5th minute	457	348	**	++	290	**	+	332	**	++
6th minute	463	348	**	++	292	**	+	332	**	++
8th minute	467	354	**	++	294	**	+	330	**	++
10th minute	450	352	**	++	296	**	+	332	**	++
12th minute	463	350	**	++	300	**	+	332	**	++
14th minute	473	350	**	++	302	**	+	332	**	++
16th minute	467	354	**	++	300	*	+	332	**	++
18th minute	470	356	**	++	306	*	+	334	**	++
20th minute	473	356	**	++	303	*	None	333	**	++
25th minute	465	352	*	++	312	*	+	338	**	++

N t t = unpaired Student's *t*-test P t t = paired Student's *t*-test
The result of unpaired t-test (determination of the statistical significance of each value as compared to placebo) is marked by asterisk.
$p < 0.01$ ** $p < 0.05$ *
The result of paired t-test (determination of the statistical significance as compared to the initial value) is marked by cross.
$p < 0.01$ ++ $p < 0.05$ +



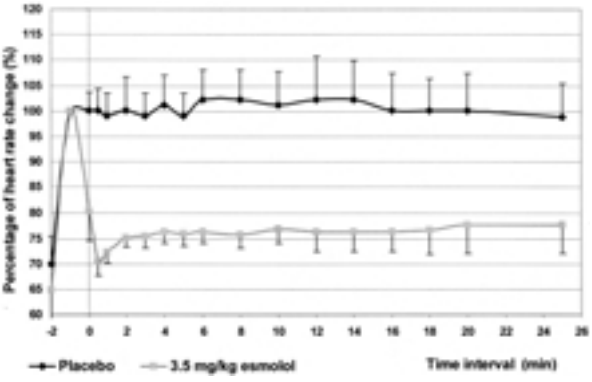
The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 5. Heart rate change (in %) following the administration of esmolol at the concentration of 1.5 mg·kg^{-1}



The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 6. Heart rate change (in %) following the administration of esmolol at the concentration of 2.5 mg·kg^{-1}



The heart rate value immediately before the administration is 100 %.
All results are presented as mean values and standard deviations.

Fig. 7. Heart rate change (in %) following the administration of esmolol at the concentration of 3.5 mg·kg^{-1}

Between the effect of the concentration 1.5 mg·kg^{-1} (heart rate decrease by 14.64 ± 10.14% against the initial value or by 14.26% against placebo) and 2.5 mg·kg^{-1} no significant difference was found. Consequently, we can conclude that the bradycardic effect is reached at the concentration of 1.5 mg·kg^{-1} and by the dose increase no stronger therapeutic effect, i.e. heart rate deeper decrease, is achieved.

The increase of concentration to 2.5 mg·kg^{-1} meant only a faster achievement of the maximum heart rate decrease and also a faster return to the initial value – 90% value of the initial status is reached in the 5th minute in concentration 2.5 mg·kg^{-1}, while with the concentration 1.5 mg·kg^{-1} the same result was seen only in the 16th minute.

The highest administered concentration (3.5 mg·kg^{-1}) manifested itself in a heart rate decrease by 8.06 ± 6.87% against the initial value, or by 8.26% against placebo.

The tested compound 44Bu has besides the bradycardic effect, also a hypotensive effect. At the administration of the dose over 3 mg·kg^{-1} the compound 44Bu induced a sharp decrease of arterial blood pressure, which led to consequent engagement of the compensation mechanisms of the organism. This phenomenon was not observed at lower concentrations (Frydrych 2003). The engagement of these compensation mechanisms attempting to increase the blood pressure by the heart rate increase offers the explanation of the lower bradycardic effect of the highest concentration tested in this experiment.

If we compare the action of the compound 44Bu and esmolol, we find that they are not different in the onset of action, but in the depth of the heart rate decrease, above all at higher concentrations. On the contrary, at the concentration of

1.5 mg·kg^{-1} no significant difference was found between the influence of the compound 44Bu and esmolol on the heart rate during the first 14 minutes. During the 25 minutes of monitoring the heart rate after the intravenous administration of esmolol was kept under the limit of 85% of the initial value, after the administration of 44Bu under the limit of 95% of the initial value.

The results of the previous experiments confirm that the compound 44Bu reduces the heart rate in the laboratory rat from the physiological level - the maximum heart rate decrease following the compound 44Bu administration at the dose of 2.5 mg·kg^{-1} was 13.00 ± 5.53% of the initial value (Bartošová et al. 2002). Isoprenaline-induced tachycardia model showed that the administration of a dose of the same concentration led to the heart rate decrease by 14.06 ± 8.43 % of the initial value. No significant differences were found between these figures.

The compound 44Bu decreases the heart rate of the same percentage regardless of the initial value of the heart rate (base line or tachycardia induced by sympatomimetic drugs). In this effect 44Bu differs from the effects of other ultrashort-acting beta blockers. All the so far existing experiments points, that heart rate decrease is probably caused not only via beta receptors and Ca^{2+} ion channels, but also via Na^{+} ion channels.

Based on the above facts, it may be assumed that the tested compound does not fully antagonize isoprenaline effect. Besides the beta-blocking activity it also possesses a partial sympathomimetic activity. However, it is also possible, that the heart rate decrease is determined only by the dromotropic effect of the compound in the myocardium, i. e. by a distinct prolongation of PQ interval. This anti-arrhythmic activity results from the compound 44Bu capability to block the fast sodium current I_{Na} and the transient outward potassium current I_{to} in cardiomyocytes (Bartošová et al. 2003).

It was experimentally documented that the newly synthesized compound 44Bu has a significant bradycardic effect at all tested concentrations. The onset of action was very fast and comparable with esmolol. Significant heart rate changes were recorded during 30 s following the intravenous administration. The lowest dosage of the tested substance (1.5 mg·kg^{-1}) proved as the most convenient because at this dose the deepest and most stable heart rate decrease was reached with a maximum of 14.64 ± 10.14%. With increasing concentration of 44Bu, the influence on the heart rate was not increased, which supports the hypothesis that the compound 44Bu has, besides a beta-sympatholytic activity, also an intrinsic sympathomimetic activity. On the contrary, with increasing concentration of esmolol its influence on the heart rate also increases.

Statistically significant heart rate change against placebo was recorded at the concentration 1.5 mg·kg^{-1} in 25 min, at concentrations 2.5 and 3.5 mg·kg^{-1} in 14 min following the intravenous administration. It was demonstrated that the ultrashort acting time of 44Bu is based on its chemical structure.

Schopnost nově syntetizovaného ultrakrátkého blokátoru beta adrenergních receptorů 44Bu antagonizovat izoprenalinem vyvolanou tachykardii – porovnání s esmololem

Cílem této práce bylo otestovat in vivo účinek tří nově syntetizovaných potenciálních ultrakrátkých β blokátorů na srdeční frekvenci laboratorního potkana. Testovaná látka byla aplikována zvířatům s indukovanou tachykardií v celkové anestézii formou intravenózního bolusu. Testovány byly dávky 1,5 mg·kg^{-1}, 2,5 mg·kg^{-1} a 3,5 mg·kg^{-1} hmotnosti zvířete a účinnost porovnána proti placebu. Pro monitorování srdeční frekvence byl použit počítačový elektrokardiograf. Statisticky významný pokles srdeční frekvence ($p < 0,05$) byl zaznamenán u všech tří testovaných dávek a to minimálně do 14. minuty od i.v. aplikace. Bradykardický účinek látky 44Bu byl porovnán s působením esmololu za stejných experimentálních podmínek. Působení látky 44Bu a esmololu se neliší v rychlosti nástupu účinku, ale v hloubce poklesu srdeční frekvence především při vyšších koncentracích. Experimentálně jsme ověřili, že látka 44Bu má vlastnosti ultrakrátce působících blokátorů beta adrenergních receptorů.

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