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DERIVATIVES OF 1-(3-AMINOPROPYL)-1H-IMIDAZOLE AS POTENTIAL LOW-TOXICITY LOCAL ANESTHETICS

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Abstract

Introduction. Aminopropylimidazole derivatives, which potentially can have various pharmacological activities and have a wide range of applications in pharmacochemistry, were selected as the object of study.

Aim. The study aimed to investigate some biological effects of new aminopropylimidazole derivatives. In this study, we investigated the acute toxicity and local anesthetic activity in an experiment on laboratory animals.

Materials and Methods. The study of the acute toxicity of the compounds was conducted on healthy, sexually mature, non-linear mice. The study of local anesthetic activity during infiltration anaesthesia was carried out using the method of Bulbring and Wajda on male guinea pigs. The tail flick method was used for the experimental study of local anesthetic activity during conduction anaesthesia.

Results. The compounds showed low toxicity, as well as a positive effect of varying degrees of expression during the study of local anesthetic activity in models of conduction and infiltration anaesthesia, exceeding the indicators of novocaine.

Conclusion. The obtained results may become the basis for further in-depth study of these compounds within the framework of expanded preclinical trials, including the study of chronic toxicity and the determination of optimal therapeutic doses, with the aim of creating new local anesthetic agents.

Key words: aminopropylimidazole derivatives, toxicity, local anaesthetic activity, conduction anaesthesia, infiltration anaesthesia.

Introduction. Pain is one of the most common complaints in people with acute and chronic diseases, which significantly reduces the quality of life of the patient [1]. Every doctor of any profile is faced with the elimination or prevention of pain syndrome. At the moment in dentistry, ophthalmology, gynaecology and surgery local anaesthetics are mostly used for temporary pain relief and are preferred to general anaesthesia because they can reduce the number of postoperative complications [2]. Local administration of anaesthetic solutions is a priority because it allows rapid anaesthesia of the area to be treated and also avoids systemic complications. Therefore, some outpatient surgeries performed under local anaesthesia require highly effective drugs for local anaesthesia to control pain syndrome [3]. However, despite the urgency of the problem, the availability of pharmacological developments in this field, and the available guidelines and recommendations on pain management, the problem is far from being solved and patients often do not receive adequate care [4].

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The use of local anesthetics in medical practice often has side effects, like many drugs, which leads to the need to create safe and effective local anesthetics [5]. Currently, the emergence of drugs with a long action and high efficiency can open up great opportunities for their use in various fields of medicine.

In clinical practice, various groups of drugs are used for pain management, among which local anaesthetics have a number of advantages because they have a variety of dosage forms, wide clinical application, relatively few complications and negligible effects on the physiological functions of the patient [6]. Thus, local anaesthetics play an indispensable role in the management of pain, and are undoubtedly among the first choices for use [7]. Local anaesthetics can help to reduce discomfort and create a favourable environment for the patient to manage pain symptoms. There is an expanding arsenal of local anaesthetics that could provide sufficient depth of analgesia for a relatively long period of time, while having minimal side effects, which could ultimately improve the quality of care [8].

Heterocycles containing azole ring system exhibit a wide range of biological properties, which include antiparasitic [9], antibacterial [10,11], antifungal [12], antimalarial [13], antituberculosis [14] and antiviral properties [15], antitumour [16], and antioxidant properties [17]. A number of studies have shown the presence of anti-inflammatory properties in imidazole compounds [18,19]. For example, a series of halogenated 1,5-diarylimidazole compounds were synthesised and their inhibitory effect on lipopolysaccharide (LPS) induced PGE2 production in RAW 264.7 cells was evaluated, among which four compounds were identified as stronger inhibitors of PGE2 production than celecoxib [20]. The results of a series of 1-aryl-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a]imidazole derivatives showed that 1-(4-methylphenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole-5,6-dione is a negative allosteric modulator (NAM) of the human μ-opioid receptor [21]. The synthesized 2-substituted-1H-phenantro [9, 10-d]imidazole compounds exhibited analgesic activity in the tail-flick model [22]. Achar et al. prepared a class of 2-methylaminobenzimidazole compounds and investigated its analgesic and anti-inflammatory activity in vivo. Among them, two compounds showed significant analgesic and anti-inflammatory activity compared to the reference nimesulide [23].

One of the pharmacological properties of imidazole derivatives is local anesthetic activity. In the studies of Yan R. et al., it was indicated that the synthesized 1,2,4,5-tetrasubstituted imidazoles showed local anesthetic activity [24]. Another study found two imidazole derivatives that were superior in activity to bupivacaine and similar in toxicity [25].

These data give us grounds to assume that the newly synthesized imidazole derivatives have local anesthetic activity. In this regard, the aim of our work was to evaluate the potential of the fragment 1-(3-aminopropyl)-1H-imidazole as a local anesthetic.

Materials and methods.

Ethical issues

All studies were approved by the Local Bioethics Commission of Asfendiyarov Kazakh National Medical University (Protocol No. 8 (114), dated 01.27.2021).

Chemical synthesis and structural analysis

For experimental study of acute toxicity and local anesthetic activity, the objects of the study were 3 azaheterocyclic derivatives with an aminopropylimidazole fragment (Figure 1), synthesized at the A.B. Bekturov Institute of Chemical Sciences.

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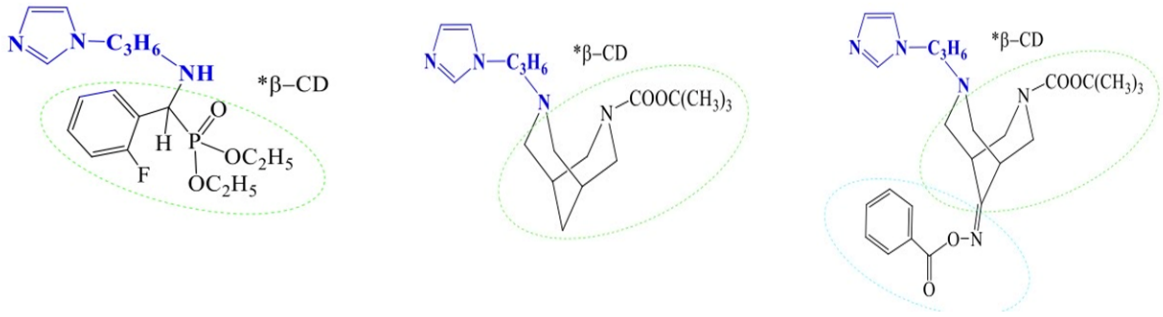

Compound A
Complex of Diethyl[(3-(1H-imidazol-1-yl)propylamino)(2-fluorophenyl)methyl]phosphonate with β-CD

Compound B
Complex of 3-(3-BOC)-7-(3 imidazolopropyl)-3,7diazabicyclo[3.3.1]nonane with β-CD

Compound C
Complex of Benzoyloxime 3-(3-BOC)-7-(3 imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD

Figure 1. Chemical structure of compounds.

The reaction progress and individuality of compounds were controlled by TLC on aluminium oxide of II degree of activity, with iodine vapour stains. IR spectra were recorded on a Nicolet 5700 FT-IR spectrometer (USA) in KBr pellets and in thin film. ^{1}H and ^{13}C NMR spectra were taken on a JNM-ECA Jeol 400 spectrometer (Japan) (399.78 and 100.53 MHz, respectively) using DMSO-d6 solvent. Chemical shifts were measured relative to the signals of the residual protons or carbon atoms of deuterated dimethyl sulfoxide.

N-[(2-Fluorophenyl)(diethyl)methyl]-3-(1H-imidazol-1-yl)propan-1-amine(1)

In a flat-bottomed conical flask equipped with a Dean-Stark trap with a reflux condenser, 2.1 ml (0.016 mol) of 1-(3-aminopropyl)-1H-imidazole in 185 ml of absolute benzene are placed. Then 3.46 ml (0.034 mol) of 2-fluorobenzaldehyde and 2.86 ml (0.022 mol) of diethyl phosphite are successively added. The mixture is stirred for 20 min at room temperature. With constant stirring, the reaction mixture is heated at the boiling point of benzene for 37 h. After distilling off the solvent, the residue is repeatedly washed with hot hexane. From the hexane fraction,N-[(2-fluorophenyl)(diethyl)methyl]-3-(1H-imidazol-1-yl)propan-1-amine**1**(3.82 g, 58%) with Rf 0.11 (Al2O3, eluent hexane: chloroform - 1:3), nD20=1.535.

Calculated for C17H25N3O3 PF: C 55.28; H 6.77; N 11.38; P 8.39.

Found: C 55.25; H 6.80; N 11.40; P 8.41.

IR spectrum, cm-1: 1457 (C=C); 1081 (CN); 1157 (P=O); 757 (PC); 1030 (C-F).

^{1}H NMR spectrum (δ, DMSO-d6): 0.92 s (6H, H-14.23), 2.09 s (2H, H-7), 2.45 s (1H, H-8ax), 2.63 (1H, H-8 eq), 2.63 s (1H, NH), 3.46-3.55 s (2H, H-13ax,22ax), 3.57-3.70 s (2H, H-13eq,22 eq), 3.87 (2H, H-6). (1H-imidazol-1-yl)propyl: 6.77, 6.96, 7.53 s (3H, CHimidazol). 7.16, 7.34, 8.09 d (4H, C6H4F).

^{13}C NMR spectrum (δ, DMSO-d6): 16.9, 17.0 (C-14, 23), 27.5, 44.0, 44.5 (C-6-8), 51.8, 61.4 (C-10, 13.22). (1H-imidazol-1-yl)propyl: 119.7, 128.2, 137.4 (CHimidazol). 115.4-162.2 (C6H4F).

COSY NMR spectrum: H8ax→H8eq, H14,23→H13,22, H7→H6.,H22ax→H22eq, H13ax→H13eq, H19→H20, H19→H18. HMQC NMR spectrum: H23.14→C23.14, H7→C7, H8ax→C8, H8eq→C8, H22ax→C22; H13ax→C13, H22eq-C22; H13eq→C13, H6→C6, H10→C10, H2→C2, H20→C20, H5→C5, H19→C19, H4→C4, H17→C17, H18→C18. HMBC NMR spectrum: H23.14→C22.13, H6→C7, H10→C15, H10→C20, H10→C20, H2→C4, H2→C5.

ComplexN-[(2-Fluorophenyl)(diethyl)methyl]-3-(1H-imidazol-1-yl)propan-1-amine (2, Compound A)

To obtain the inclusion complex, mix solutions of 2 g (0.005 mol)N-[(2-Fluorophenyl)(diethyl)methyl]-3-(1H-imidazol-1-yl)propan-1-aminein 50 ml of ethyl alcohol and 6.14 g (0.005 mol) of β-cyclodextrin in 80 ml of distilled water. The mixture is placed in a drying oven, ethanol and water are evaporated at 50-550C. The inclusion complex of diethyl (((3-(1H-imidazol-1-yl)propyl)amino)(2-fluorophenyl)methyl)phosphonate with β-cyclodextrin 2 (7.88 g, 97%) is obtained as a white powder.

Calculated for C59H95N3PFO38: C 47.10; H 6.32; N 2.80; P 2.06.

Found: C 47.30; H 6.30; N 2.78; P 2.08.

Experimental animals

To study the safety and local anaesthetic activity of imidazole derivatives, we used conventional methods recommended by the manual on experimental (preclinical) study of new pharmacological substances by A. N. Mironov (2012) [26]. Experimental work was performed on outbred white mice (8-9-week-old), guinea pigs (mature animals) and rats (7-8-week-old). All laboratory animals were previously quarantined for 2 weeks. The animals were housed in specialized cages under controlled hygienic conditions at a temperature of 25 ± 2 °C, with adequate ventilation and a natural 12-hour light/dark cycle. They had unrestricted access to clean drinking water and standardized feed appropriate for each species. Animals were individually identified using permanent marker labeling to ensure accurate tracking throughout the study. All experimental procedures involving animals were conducted in accordance with the Order of the Minister of Health of the Republic of Kazakhstan dated December 11, 2020 No. KP DSM-255/2020 “On approval of the rules for conducting preclinical (non-clinical) studies and requirements for preclinical bases to assess the biological effect of medical devices”, as well as the rules of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” and Directive 2010/63/EU of the European Parliament and Council of the European Union on the protection of animals used for experimental and other scientific purposes. Experimental procedures involving animals were conducted in accordance with internationally accepted principles for the care and use of laboratory animals and complied with the relevant national regulations.

Acute toxicity testing

Acute toxicity studies of the investigated compounds were carried out on healthy sexually mature outbred mice of both sexes of the same age by subcutaneous administration (n = 78, weight 18-20 g) [26]. Laboratory animals were divided into groups of 6 animals (3 female mice and 3 male mice) each randomly. Aqueous solutions of the tested compounds in 3 different concentrations (Table 2) and reference preparations (lidocaine, trimecaine, procaine) were administered to animals once subcutaneously in the lateral surface of the body. The total duration of observation of the animals was 14 days. During the observation period the general condition of animals was recorded, in particular, behavioural characteristics, intensity and character of motor activity, presence and character of convulsions, coordination of movement, tone of skeletal muscles, reaction to tactile, pain, sound and light stimuli, condition of hair and skin, colour of mucous membranes, tail position, quantity and consistency of faecal masses, feed.

Local anesthetic activity in infiltration anaesthesia

A study of local anesthetic activity during infiltration anaesthesia was conducted using the Bulbring and Wajda method on male guinea pigs [27]. Laboratory animals were randomly divided into groups of 6 animals each to study one compound. Freshly prepared 0.5% solutions of the test drug in a volume of 0.25 ml were injected intradermally into the back of each animal, after removing the hair from it; freshly prepared isotonic solutions of the test compound were injected intradermally at 4 points at the corners of a square with a side of 3 cm. Local anesthetic activity was assessed 6–8 times for each of the selected concentrations. Sensitivity at the

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injection site was determined by touching with an injection needle in a series of 6 touches at intervals of 3–4 s, every 5 min, for 30 min. For each experimental series, the following parameters were assessed: the total number of needle stimulations that did not induce a skin twitch response during a 30-minute observation period (anaesthesia index), the duration of complete anaesthesia, and the total duration of anesthetic action.

Local anesthetic activity in conduction anaesthesia

The tail flick method was used for the experimental study of local anaesthetic activity in regional anaesthesia. Modified method "tail flick" [28], was used for the experimental study of local anaesthetic activity in regional anaesthesia. The study was carried out on outbred white male rats. Laboratory animals were divided into groups randomly with 6 animals in each group for the study of one compound. The principle of the method is to record the latent period of tail retraction during thermal exposure of its middle part by a focused light beam of an optoelectronic algesimeter TF-003 before and after anaesthesia. The intensity of the thermal nociceptive effect was adjusted so that the initial tail twitch responses proceeded with a latent period between 3 and 6 seconds. Initially, the threshold of pain sensitivity was determined. Then, a solution of test compound and reference drug in a volume of 1 ml was injected evenly on the four sides of the root of the tail of the rat. After administration of test compound and reference drugs, retesting was performed for a specific time interval. An increase in the latency period of the tail wagging reflex by a factor of 2 will be evaluated as complete anaesthesia. Compounds and reference drugs (lidocaine, trimecaine, procaine) were compared in terms of time of onset of anaesthesia, duration of complete anaesthesia and total duration of anaesthetic effect of the drug.

Statistical analysis

The median lethal dose (LD_{50}), expressed as the mean value ± standard error, was calculated based on the experimental results. LD_{50} values were estimated using the QuestGraph™ LD_{50} Calculator (AAT Bioquest, Inc. https://www.aatbio.com/tools/ld50-calculator). All data are presented as mean ± standard error of the mean (SEM) or standard deviation (SD), as specified. Statistical analyses were performed using SPSS 27.0 software (IBM, USA). To assess the precision of the median lethal dose (LD50) estimation, the 95% confidence interval (95% CI) was calculated using Student's *t*-test for small sample sizes. The calculation was performed according to the following formula:

$$95\%CI=LD50\pm t\times SE95\%CI=LD50\pm t\times SE, \quad (1)$$

where *LD50* is the median lethal dose, *SE* is the standard error of the mean, and *t* is the critical value of Student's *t*-distribution for a two-tailed 95% confidence interval with $n - 1$ degrees of freedom. For $n = 6$, the value $t = 2.571$ was used [29].

Pairwise comparisons were performed using Student's t-test followed by Holm–Bonferroni correction for multiple testing. All quantitative data obtained from the experimental series were assessed for compliance with normal distribution using the Shapiro–Wilk test, which has high sensitivity for small sample sizes.

Results

Synthesis of aminopropylimidazole derivatives

We have found that bicyclic derivatives with an imidazole fragment have growth-stimulating activity (Compound B) [30] and toxicity to tumor cells and the ability to activate polyamine oxidase in liver lysates (Compound B) [31]. The difference is in the bicyclic part – (benzoyloxy)imino groups at the 9-position of the bispyridine ring in Compound B and Compound C affected bioactivity. It should be noted that the pharmacological potential is far

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from exhausted, in particular, including local anesthetic activity. In addition, the "replacement" of the bicyclic part with a phosphonate fragment seems interesting. Therefore, a new α-aminophosphonate was synthesized based on 1-(3-aminopropyl)-1H-imidazole under the conditions of the Kabachnik-Fields reaction. The interaction of 3-(1H-imidazol-1-yl)propan-1-amine with 2-fluoraldehyde and diethyl phosphite in benzene at 70-90 °C yielded the target α-aminophosphonate (58%), which is a thick, mass-like product. β-cyclodextrin was used to encapsulate the aminophosphonate molecule (Figure 2).

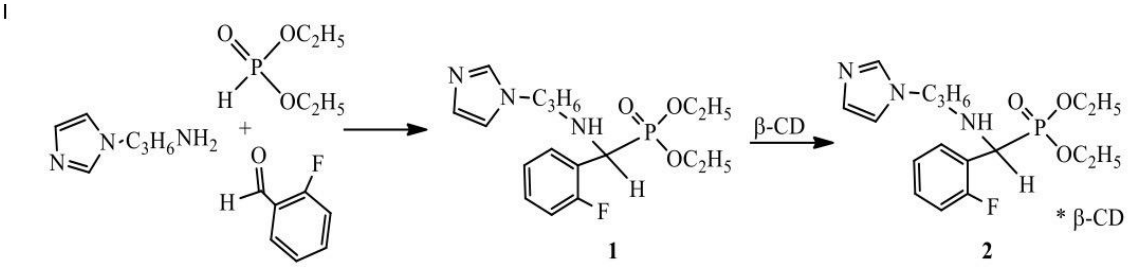

Figure 2. Synthesis of aminopropylimidazole derivatives.

The structure of the compounds was confirmed by 1H, 13C NMR methods. In the 1H NMR spectrum of the Compound A is characterized by the presence in the strong-field region of the spectrum at 0.92 ppm of a six-proton singlet signal of methyl protons H-14,14,14,23,23,23 of two ethoxy groups. Methylene protons H-7,7 of the imidazolepropyl fragment appeared as a two-proton singlet signal at 2.09 ppm. Methylene protons H-8ax and H-8eq resonated with two singlets at 2.45 and 2.63 ppm, respectively. Methylene protons H-6,6 appeared as a two-proton singlet at 3.87 ppm. The quaternary proton H-10 appeared as a doublet signal at 4.44 ppm. Due to the presence of proton-proton exchange processes with solvent molecules, protons H-9 appeared as a broadened singlet signal at 5.28 ppm. In the imidazole ring, protons H-5, H-4, and H-2 appeared as singlets at 6.77, 6.96, and 7.53 ppm, respectively. Fluorophenyl protons H-17 and H-19 resonated as a single-proton doublet at 7.16 ppm, and protons H-18 and H-20 appeared as singlets at 7.34 and 8.09 ppm, respectively.

In the 13C NMR spectrum of the compound1 signals of ethoxy groups appeared at 16.93 and 16.98 (C-14,23) and 61.38 (C-13,22) ppm. The tertiary carbon atom C-10 appeared at 51.79 and 53.14 ppm. The imidazolepropyl carbon atoms resonated at 27.47 (C-7), 43.98 (C-6), 44.48 (C-8), 119.66 (C-4), 128.19 (C-5) and 137.40 (C-2) ppm. The carbon atoms of the aromatic fragment resonated at 115.41 (C-17), 121.32 (C-15), 130.84 (C-20,18) and 159.73 and 162.17 (C-16) ppm. Structure of the Compound A was also confirmed by the methods of one-dimensional DEPT spectroscopy and two-dimensional NMR COSY (1H-1H), HMQC (1H-13C) and HMBC (1H-13C) spectroscopy, which makes it possible to establish spin-spin interactions of homo- and heteronuclear nature. In the 1H-1H COSY spectra of the compound, spin-spin correlations are observed through three bonds of protons of neighboring methyl-methylene, methylene-methylene and methine-methine aliphatic and aromatic groups: H8ax-H8eq (2.47, 2.63 and 2.63, 2.47), H14,23-H13,22 (0.91, 3.54 and 3.54, 0.91), H7-H6 (2.08, 3.85 and 3.85, 2.08), H22ax-H22eq; H13ax-H13eq (3.48, 3.60 and 3.60, 3.48), H19-H20 (7.13, 7.30 and 7.30, 7.13), H19-H18 (7.14, 8.07 and 8.07, 7.14) ppm.

Heteronuclear interactions of protons with carbon atoms through one bond were established by 1H-13C HMQC spectroscopy for the following pairs present in the compound: H23,14-C23,14 (0.90, 17.10), H7-C7 (2.07, 27.70), H8ax-C8 (2.45, 44.42), H8eq-C8 (2.62, 44.62), H22ax-C22; H13ax-C13 (3.49, 61.95), H22eq-C22; H13eq-C13 (3.60, 61.75), H6-C6 (3.87, 44.01), H10-C10 (4.43, 52.37), H2-C2 (7.50, 137.38), H20-C20 (7.31, 130.86), H5-C5

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(6.75, 128.82), H19- C19 (7.13, 125.15), H4-C4 (6.94, 120.26), H17-C17 (7.15, 115.98), H18-C18 (68.08, 130.86) ppm.

Heteronuclear interactions of protons with carbon atoms through two or more bonds were established using 1H-13C HMBC spectroscopy for the following pairs present in the compound: H23,14-C22,13 (0.90, 61.42); H6-C7 (3.84, 27.71); H10-C15 (4.41, 121.36), H10-C20 (4.42, 130.72), H10-C20 (4.41, 160.69); H2-C4 (7.50, 119.48), H2-C5 (7.50, 128.62) ppm.

Acute toxicity evaluation

Compounds and comparison preparations were administered in 3–4% solutions, depending on the dose, in a volume not exceeding 1 ml. The results of the studies are shown in Tables 1, 2.

Table 1. Acute toxicity of aminopropylimidazole derivatives for subcutaneous administration.

No.	Compound, drug	LD_{50}±SE, mg/kg	95% confidence interval, mg/kg
1	Compound A	1287±31.9 *	1204.99–1369.01
2	Compound B	901±20.3 *	848.8–953.2
3	Compound C	930±17.78*	884.3–975.7
4	Lidocaine	230±35.7	
5	Trimecaine	375±3.1	
6	Procaine	480±1.0	

Notes: Data were reported as means ±SE (n=6). * P<0.001 compared to all reference drugs (t-test).

Table 2 . Toxicity data of compounds A, B, C in mice.

Compounds	Number of animals, goal		Deaths %
	Total	Deaths	
		Compound A	
800 mg/kg	6	0	0
1000 mg/kg	6	1	16,6
1300 mg/kg	6	3	50
		Compound B	
800 mg/kg	6	1	16,6
1000 mg/kg	6	5	83,3
1200 mg/kg	6	6	100
		Compound C	
800 mg/kg	6	0	0
1000 mg/kg	6	5	83,3
1200 mg/kg	6	6	100

* Dosages were selected according to the mortality of the animals in each group.

When administered subcutaneously, Compound A at a dose of 800 mg/kg did not produce any signs of intoxication. With dose escalation to 1000 mg/kg, clear signs of intoxication were observed. Toxic effects appeared after 10–12 hours and were manifested by general depression in the animals: mice showed lethargy, reduced locomotor activity, hypodynamia, decreased appetite, and a 5–10% reduction in body weight, which recovered after 24 hours. One mouse died. At a dose of 1300 mg/kg, no response to external stimuli was observed; respiration initially became rapid and shallow, followed by deep and convulsive breathing, and tonic–clonic seizures developed. Death in three mice occurred 12–24 hours after the initial cessation of respiration.

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Following administration of Compound B (800 mg/kg), the first signs of intoxication appeared within 30–60 minutes. In animals, convulsive muscle twitching, episodes of apnea, and changes in behavioral activity were gradually observed 30–40 minutes after administration. Subsequently, locomotor activity gradually recovered, respiration normalized, and within 5–6 hours the animals returned to baseline activity levels prior to compound administration. Complete restoration of physiological parameters occurred within 24 hours. At doses of 1000 and 1200 mg/kg, 5 and 6 deaths, respectively, were recorded within 12 hours, characterized by respiratory arrest.

After subcutaneous administration of Compound C, within the first minutes at a dose of 800 mg/kg, laboratory animals exhibited drowsiness, ataxia, tremor and weakness of the limbs, and convulsions, followed by respiratory depression. No significant changes in body weight were observed. Recovery occurred after 10–12 hours, although one mouse died. At increased doses of 1000 and 1200 mg/kg, adynamia was observed in mice. Immediately after administration, convulsions occurred lasting 20–30 minutes, after which the animals exhibited deep breathing. Death occurred 24 hours after administration.

It should be noted that the clinical manifestations observed in laboratory animals, including their behavioral responses and pathological changes, did not differ depending on sex.

After administration of the compound, the animals were continuously monitored for the first 4 hours and subsequently observed daily for 14 days. The study did not involve the induction of pain; therefore, anesthesia was not applied. Animals that reached a terminal state or exhibited severe signs of distress were humanely euthanized under general anesthesia (Zoletil–Xylazine). Euthanasia was performed using Zoletil–Xylazine anesthesia followed by cervical dislocation.

After euthanasia, macroscopic examination of the liver, kidneys, and lungs was performed, including assessment of organ size, color, consistency, and the presence of pathological changes. Histology was presented in the high-dose groups, where pronounced changes were observed in the lungs, liver, and kidneys.

During the investigation of Compound A, administration at a low dose resulted in focal serous hepatitis in the liver and hydropic degeneration in the kidneys. This type of irreversible degenerative change may lead to acute renal failure, which can be accompanied by pronounced pulmonary manifestations such as focal pneumonitis and pulmonary edema, potentially resulting in death. At higher doses, focal hepatic alterations characterized by venous congestion and protein dystrophy were observed. In the lungs, venous congestion accompanied by erythrodiapedesis was detected, while cortical necronephrosis was observed in the kidneys. In this regard, acute renal failure can be considered the probable cause of death.

In the case of Compound B, histological examination of target organs revealed venous congestion in the liver, microcirculatory venous congestion accompanied by erythrodiapedesis in the lungs, and necronephrosis in the kidneys, which ultimately led to death.

For Compound C, histological analysis of target organs demonstrated protein dystrophy in the liver as well as protein dystrophy and venous congestion in the kidneys. In the lungs, focal hemorrhages in the alveoli and focal emphysematous changes were observed.

During the histopathological examination, various changes in the major organs caused by the tested compounds were identified. (Figure 3).

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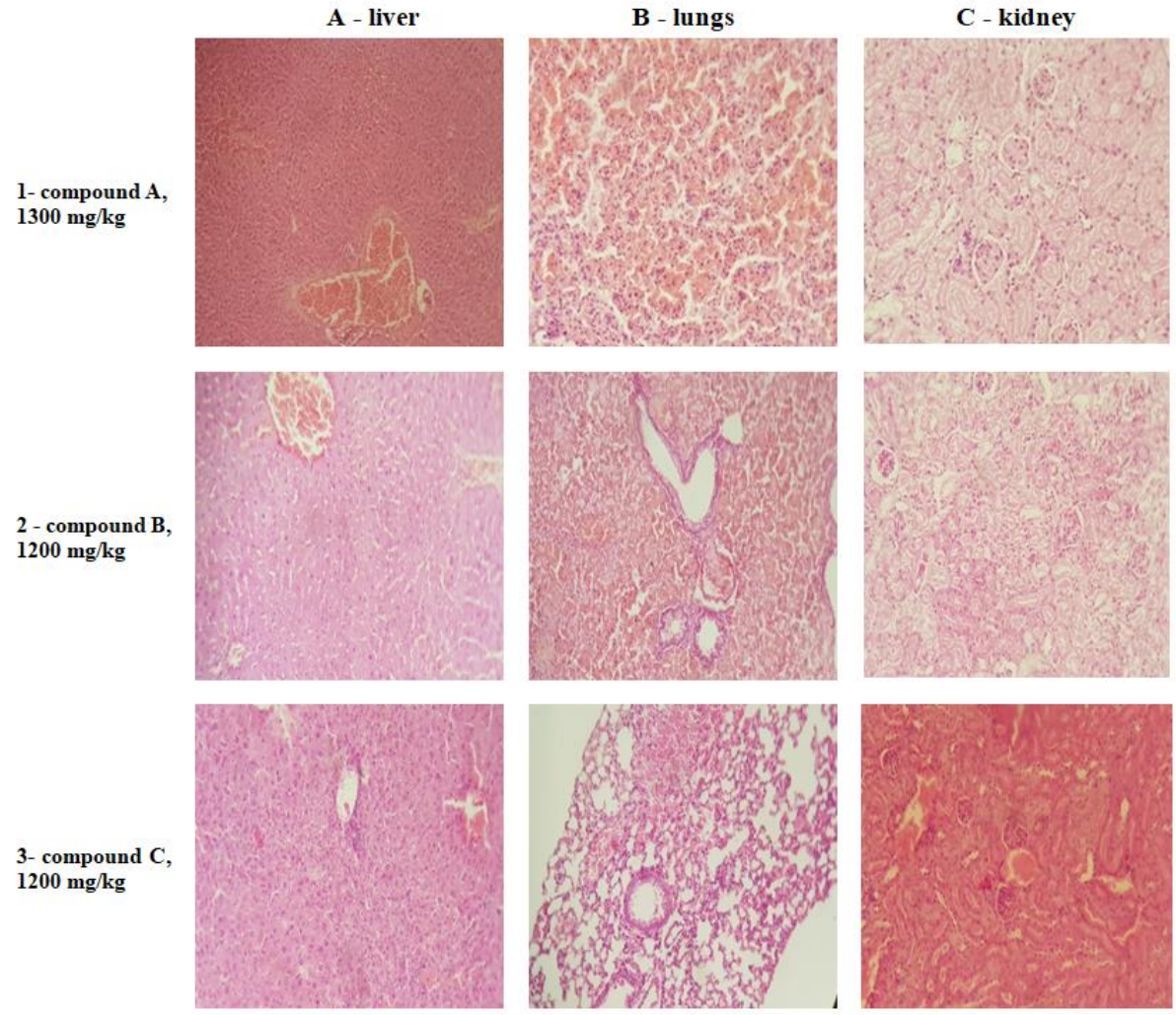

Figure 3. Histopathological examination of target organs. Hematoxylin and eosin staining, x400: 1A – hepatic venous fullness, protein dystrophy; 1B – venous fullness with erythrodiapedesis; 1C – cortical renal necronephrosis. 2A – venous liver fullness; 2B – venous fullness with erythrodiapedesis; 2C – renal necronephrosis. 3A – hepatic protein dystrophy; 3B – small focal bleeding in the alveoli, small focal emphysema of the lungs; 3C – protein dystrophy, venous renal fullness.

Evaluation of local anesthetic effect in infiltration anaesthesia

When studying infiltration anaesthesia, the depth of anaesthesia in 'anaesthesia indices', the duration of complete anaesthesia and the total duration of the anaesthetic effect were determined. Depth of local anaesthetic effect – weakening of nociceptive reaction caused by the substance (up to its complete disappearance) in comparison with the initial values of this reaction in response to nociceptive stimulation of the tissue area locally affected by the substance. Full anaesthesia – increase in the latency period by at least 2 times (by 100%). Duration of anaesthesia – the period of time from the development of local anaesthesia to its disappearance.

The obtained experimental data showed that the substances are effective to varying degrees in infiltration and conduction anaesthesia. The results of the study of the local anesthetic activity of aminopropylimidazole compounds in infiltration anaesthesia are shown in Figures 4 and 5.

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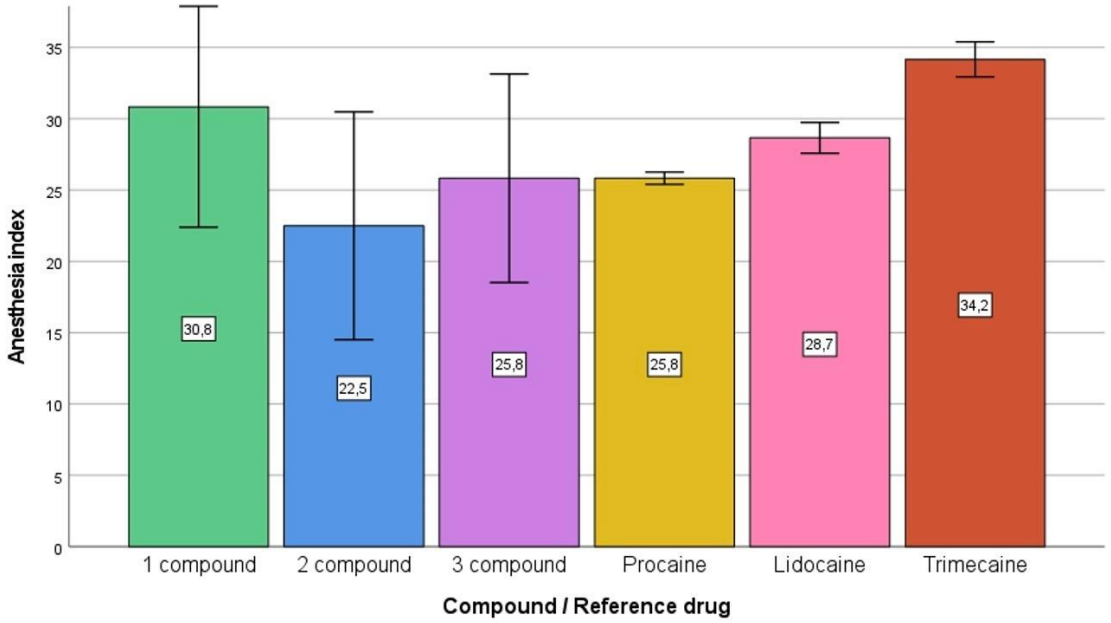

Figure 4. Anaesthesia index of compounds during infiltration anaesthesia (0.5% aqueous solutions). Notes: Data are reported as means±SD (n=6), t-test, Holm-Bonferroni correction. A – Anaesthesia index (max-36).

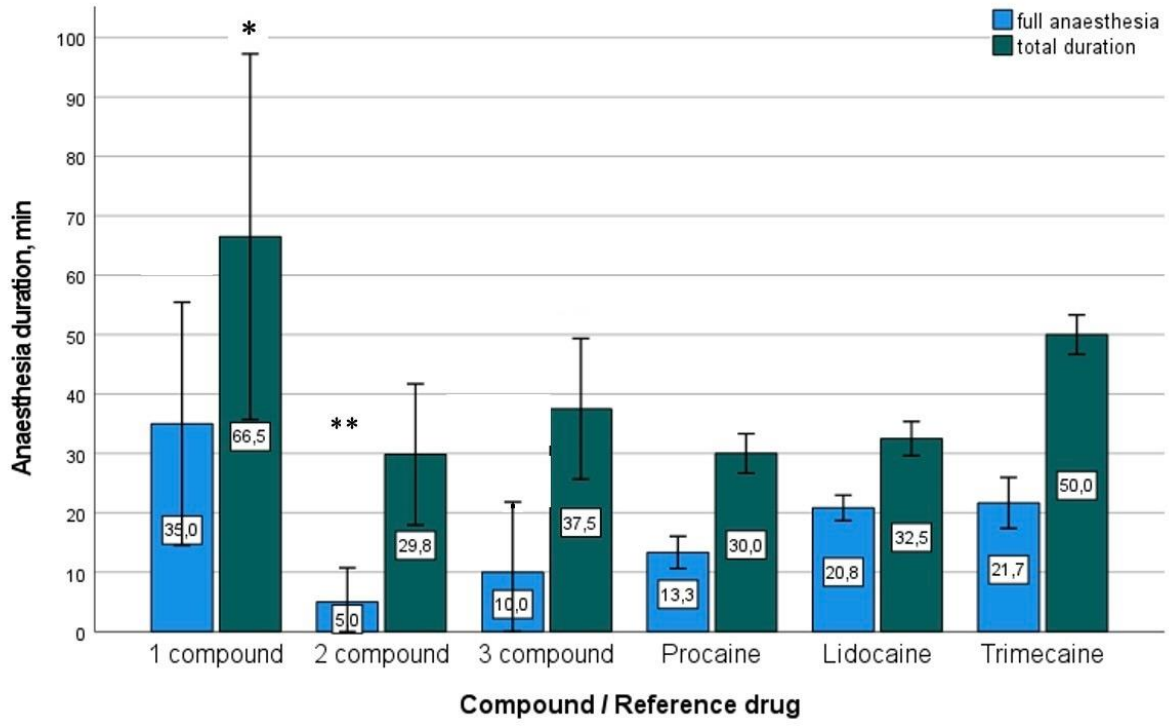

Figure 5. Local anesthetic activity parameters of 0.5% solutions (infiltration anaesthesia model). Notes: Data are reported as means±SD (n=6), t-test, Holm-Bonferroni correction: *P<0.05 compared to procaine. **P<0.001 compared to trimecaine.

According to Figures 4 and 5, it can be noted that Compound A (the complex of diethyl[(3-(1H-imidazol-1-yl)propylamino)(2-fluorophenyl)methyl]phosphonate with β-CD)

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at a concentration of 0.5% was the most effective in terms of the total duration of anaesthesia compared to procaine.

Evaluation of local anesthetic effect in conduction anaesthesia

When modelling conduction anaesthesia, the compound benzoyloxime 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (compound C), which induced complete anaesthesia (complete anaesthesia index 38.3), was slightly inferior to trimecaine ($p>0.05$) and superior to procaine ($p>0.05$), but inferior to lidocaine. The duration of action was 62 minutes, which was superior to trimecaine and procaine but inferior to lidocaine. It is likely that the presence of the benzoyloxime group contributes to the local anaesthetic activity observed in conduction anaesthesia. Table 4 summarises the results of the study.

Table 4. Local anesthetic activity parameters of 1% solutions (conduction anaesthesia model).

Compound, reference drug	Duration of deep anaesthesia, min	Total duration of action, min
Compound A	-	22.8±1.48*
Compound B	-	6.67±1.18**
Compound C	38.3±5.55	62.0±4.84
Trimecaine	47.3±8.4	56.9±12.8
Lidocaine	65.0±18.4	90.0±18.4
Procaine	35.2±7.1	42.3±13.6

Notes: Data were reported as means ±SE (n=6). * $P<0.05$ compared to trimecaine,
** $P<0.05$ compared to trimecaine, novocaine (t-test, Holm-Bonferroni correction).

The complex of diethyl [(3-(1H-imidazol-1-yl) propyl-amino) (2-fluorophenyl)methyl]phosphonate with β-CD (compound A) and 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1.1]nonane with β-CD (compound B) at 1% concentration did not show complete anaesthesia. The duration of action was 22.8 min for compound A and 6.67 min for compound B.

Discussion. According to the literature imidazoles are low toxic [32, 33], which was confirmed by this experiment. The toxicity results showed that diethyl[(3-(1H-imidazol-1-yl)propyl-amino)(2-fluorophenyl)methyl]phosphonate with β-CD (compound A) was the least toxic: The LD50 was 1287 mg/kg. This value was 5.3 times higher than lidocaine, and trimecaine 3.2 times and procaine 2.5 times. Unlike other groups, the presence of 2-fluorophenylmethyl phosphonate in the composition of the group possibly reduces the toxicity of this compound. This is consistent with the data of a number of studies on the synthesis of new aminophosphonates containing fluorine in its structure, showed low toxicity. Thus, in the studies of Yu VK et al. and Singh I. et al. synthesised dimethyl[(4-benzhydrylpiperazin-1-yl)(p-o-fluoro-phenyl)methyl]phosphonates were less toxic compared to reference drugs – trimecaine, lidocaine and procaine [34, 35].

The indicators for compounds C were also of low toxicity: the LD50 for 3-(3-BOC)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (compound B) was 901 mg/kg, and for benzoyloxime 3-(3-BOC)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (compound C) it was 930 mg/kg. These values were 3 times higher than those of lidocaine and 2 times higher than those of trimecaine and procaine. Both compounds contained complexes of imidazolopropyl with diazabicyclononane and β-CD, which likely contributes to their low toxicity. In Grecu M. et al. studies have demonstrated the role of complexes with β-CD in improving the safety profile of compounds [36]. Between compounds C and B, Compound C (930 mg/kg) was the least toxic, slightly surpassing compound B (901 mg/kg),

most likely due to the presence of a benzoyloxime group in its structure. Thus, it can be assumed that the presence of imidazole group in the structure of molecules helps to reduce toxicity.

A study of the local anesthetic activity of imidazole derivatives in infiltration anaesthesia model showed that compound A is higher than procaine and lidocaine in terms of anaesthesia index, less than trimecaine. The complete anaesthesia index of this compound exceeded the corresponding parameters of the reference drugs; however, no statistically significant differences were found ($p>0.05$). In terms of the total duration of anaesthesia, this substance exceeded the corresponding parameter of procaine by twofold. This is probably due to the presence of 2-fluorophenylmethyl phosphonate in the structure of the fragment, which led to an increase in the duration of complete anaesthesia and general anaesthesia. In a study by Perrone MG. et al. some fluoromethyl substituted compounds had biological activity as analgesics [37]. Also, Almasirad A. et al. determined that the phenyl moiety can enhance the analgesic activity of triazole derivatives [38]. These literatures show the analgesic activity of compounds that contain fluorophenyl fragments.

In the study of local anaesthetic activity on the model of infiltration anaesthesia the least active was 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1.1]nonane with β-CD (compound B), which was inferior to lidocaine, procaine and trimecaine in terms of anaesthesia index, complete and duration of anaesthesia. The activity of benzoyloxime 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (compound C) occupies an intermediate position in comparison with other studied compounds: in terms of the anaesthesia index, it was comparable to procaine and inferior to the other two reference drugs ($p>0.05$). In terms of the general anaesthesia parameter, this compound was inferior to trimecaine but slightly superior to lidocaine and procaine; however, no statistically significant differences were found. Compound C showed lower values of complete anaesthesia compared to all reference drugs ($p>0.05$). According to the results obtained during infiltration anaesthesia on guinea pigs, all compounds showed positive results, slightly inferior to the comparison drugs.

Despite the absence of statistically significant differences in the mean values of the duration of effect, the obtained data indicate a pronounced tendency toward a longer local anaesthetic action of the studied compounds. It should be taken into account that the absence of statistically significant differences in a number of comparisons may be associated with the high variability of biological responses and the small sample size ($n=6$), which is typical for preclinical studies of local anaesthetic activity. Under such conditions, the p-value may not fully reflect the magnitude of the pharmacological effect; therefore, additional evaluation of the effect size is of particular importance for the interpretation of preclinical study results.

In study of the local anaesthetic activity of aminopropylimidazole derivatives in conduction anaesthesia model the least effective was 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1.1]nonane with β-CD (compound B), which unlike the other two compounds lacks fluorophenylmethyl phosphonate or benzoyloxime groups. It should be noted that diethyl[(3-(1H-imidazol-1-yl)propyl-amino)(2-fluorophenyl)methyl]phosphonate with β-CD (compound A) is low-toxic and most active in conduction anaesthesia, possibly due to the presence of the fragment 2-fluorophenylmethyl phosphonate in the molecular structure. Compound C showed positive result in conduction anaesthesia and was also low toxic compared to the reference drugs. The molecule of this compound has a complex of benzoyloxime and imidazolopropyl with diazabicyclononam with β-CD. The presence of biological effect of this complex was confirmed in other studies. Thus, as a result of biological screening Malmakova A. et al. found that the complex of O-benzoyloxime 3-(2-ethoxyethyl)-7-cyclopropylmethyl-3,7-diazabicyclo[3.3.1.1]nonan-9-one with b-cyclodextrin shows high analgesic activity and causes complete analgesia [39]. Also in another study by the same scientists, the activity of complexes of benzoyloxime and diazabicyclonam with β-CD was also

with other compounds, for example, O-benzoyloxime 3-(3-ethoxypropyl)-7-[2-(piperazin-1-yl)ethyl]-3,7-diazabicyclo[3.3.1]nonan-9-one in a series of experiments on models of infiltration and conduction anaesthesia markedly exceeded the activity of reference drugs in a number of indicators [40].

In summary, only one compound benzoyloxime 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1.1]nonane with β-CD (compound C) exceeded procaine and trimecaine in terms of duration of anaesthesia in the conduction anaesthesia model, the other compounds were lower than the reference drugs in all parameters.

Conclusion. Our experimental studies have shown that the studied modified aminopropylimidazole derivatives are low toxic substances. The difference in chemical structure did not significantly affect the degree of toxicity of the studied compounds. The least toxic was the complex of diethyl[(3-(1H-imidazol-1-yl) propyl-amino (2-fluorophenyl)methyl]phosphonate with β-CD (compound A). The study of local anaesthetic activity on the model of infiltration anaesthesia revealed the most active compound - diethyl[(3-(1H-imidazol-1-yl)propyl-amino)(2-fluorophenyl)methyl)methyl]phosphonate with β-CD (Compound A), the parameters of which by duration of complete anaesthesia and total action slightly exceeded procaine, and by the parameter of complete anaesthesia is close to the corresponding parameters of trimekaine and lidocaine.

Experimental studies during conduction anaesthesia showed that the most effective was the compound of benzoyloxime 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (Compound C), which was slightly higher than procaine in terms of complete anaesthesia and higher than procaine and trimecaine in terms of total anaesthesia.

Thus, diethyl [(3-(1H-imidazol-1-yl)propyl-amino)(2-fluorophenyl)methyl]phosphonate with β-CD (compound A) and benzoyloxime 3-(3-boc)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane with β-CD (Compound C) are the most promising lead compounds for further preclinical evaluation.

Conflict of interest. The authors declare no conflict of interest.

Authors' contribution. Concept, D. S., E. S. and T. N.; methodology, A. K., G. K. and Z. B.; validation and formal analysis, M. K.; investigation, D. S., A. M., M. K. and V. T.; resources, E. S. and T. N.; data curation, E. S., V. Y. and M. B.; writing – original draft preparation, D. S.; writing – review & editing, E. S.; visualization, D. S.; supervision, M. K.; project administration, E. S. All authors have read and agreed to the published version of the manuscript.

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1-(3-АМИНОПРОПИЛ)-1Н-ИМИДАЗОЛДЫҢ ТУЫНДЫЛАРЫ ТӨМЕН УЫТТЫ ЖЕРГІЛІКТІ АНЕСТЕТИКТЕР РЕТІНДЕ

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Түйіндеме

Кіріспе. Зерттеу нысаны ретінде әр түрлі фармакологиялық белсенділікке ие және фармакохимияда кең ауқымды қолдану мүмкіндігі бар аминопропилимидазол туындылары таңдалды.

Мақсаты. Жұмыстың мақсаты жаңа аминопропилимидазол туындыларының кейбір биологиялық әсерін зерттеу болды. Бұл зерттеуде біз зертханалық жануарларға жасалған экспериментте жедел уыттылық пен жергілікті анестезияның белсенділігін зерттедік.

Материалдар мен әдістер. Қосылыстардың жедел уыттылығын зерттеу сау, жыныстық жетілген, сызықты емес тышқандарда жүргізілді. Инфильтрациялық анестезия кезінде жергілікті жансыздандыру белсенділігін зерттеу теңіз шошқаларының еркектеріне Bulbring және Wajda әдісін қолдану арқылы жүргізілді. Өткізгіштік

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анестезия кезіндегі жергілікті анестезияның белсенділігін эксперименттік зерттеу үшін «құйрықты тартып алу» әдісі қолданылды.

Нәтижелер. Қосылыстар төмен уыттылықты көрсетті, сонымен қатар өткізгіштік және инфильтрациялық анестезия үлгілерінде жергілікті жансыздандыру белсенділігін зерттеу кезінде новокаин көрсеткіштерінен асып түсетін әртүрлі дәрежелі оң әсерді көрсетті.

Қорытынды. Алынған нәтижелер жаңа жергілікті анестетиктерді жасау мақсатында созылмалы уыттылықты зерттеуді және оңтайлы емдік дозаларды анықтауды қоса алғанда, кеңейтілген клиникаға дейінгі зерттеулер шеңберінде осы қосылыстарды одан әрі терең зерттеуге негіз бола алады.

Түйінді сөздер: аминопропилимидазол туындылары, уыттылық, жергілікті жансыздандырғыш белсенділік, өткізгіштік анестезия, инфильтрациялық анестезия.

ПРОИЗВОДНЫЕ 1-(3-АМИНОПРОПИЛ)-1Н-ИМИДАЗОЛА КАК ПОТЕНЦИАЛЬНЫЕ МАЛОТОКСИЧНЫЕ МЕСТНЫЕ АНЕСТЕТИКИ

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Аннотация

Введение. В качестве объекта исследования были выбраны производные аминопропилимидазола, которые потенциально могут обладать различной фармакологической активностью и имеют широкий спектр применения в фармакохимии.

Цель. Целью работы было исследование некоторых биологических эффектов новых производных аминопропилимидазола. В данном исследовании мы изучали острую токсичность и местноанестезирующую активность в эксперименте на лабораторных животных.

Материалы и методы. Изучение острой токсичности соединений проводилось на здоровых, половозрелых, нелинейных мышах. Изучение местной анестезирующей активности при инфильтрационной анестезии проводилось методом Бульбринга и Вайда на самцах морских свинок. Для экспериментального изучения местной анестезирующей активности при проводниковой анестезии использовался метод отдергивания хвоста.

Результаты. Соединения продемонстрировали низкую токсичность, а также положительный эффект различной степени выраженности при изучении местной анестезирующей активности в моделях проводниковой и инфильтрационной анестезии, превосходящий показатели новокаина.

Заключение. Полученные результаты могут стать основой для дальнейшего углубленного изучения этих соединений в рамках расширенных доклинических исследований, включая изучение хронической токсичности и определение оптимальных терапевтических доз с целью создания новых местных анестезирующих средств.

Ключевые слова: производные аминопропилимидазола, токсичность, местная анестезирующая активность, проводниковая анестезия, инфильтрационная анестезия.