



On local anesthetic action of some dimethylacetamide compounds

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Academic editor: Mikhail Korokin ♦ Received 1 October 2018 ♦ Accepted 6 November 2018 ♦ Published 2 December 2018

Citation: Novikov AV, Blinova EV, Semeleva EV, Karakhanjan KM, Mironov MA, Blinov DS, Krainova YuS, Pakhomov DV, Vasilkina OV, Samishina EA (2018) On local anesthetic action of some dimethylacetamide compounds. Research Results in Pharmacology 4(4): 1–8. <https://doi.org/10.3897/rrpharmacology.4.31440>

Abstract

The **study aim** was to explore local anesthetic properties of some tertiary and quaternary derivatives of dimethylacetamide.

Materials and methods. The study was performed on white laboratory mice and rats of both sexes, male Agouti guinea pigs, and isolated sciatic nerves of lake frog. In the focus of the study there were two quaternary and eight tertiary compounds of dimethylacetamide with substituted anion with some amino and carbonic acids residue. A local anesthetic property was predicted by computational analysis. Acute toxicity of the most promising substances was studied in mice through subcutaneous route. Local anesthetic activity of tertiary compounds LKhT-3-00, LKhT-4-00 and quaternary LKhT-12-02 was studied on models of terminal, **infiltration** and conduction anesthesia. The influence of substances on mixed nerve conduction was investigated on lake frog's isolated sciatic nerves.

Results and discussion. The greatest probability of the local anesthetic activity during computational analysis was estimated for the tertiary derivatives of dimethylacetamide LKhT-3-00 and LKhT-4-00 and for the quaternary compound LKhT-12-02. According to their toxicological profile, the compounds belong to moderately toxic substances (class 3). On the model of terminal and **infiltration** anesthesia, substances LKhT-3-00 and LKhT-4-00 at concentrations of 0.5–1% rapidly cause deep and prolonged anesthesia. On the models of conduction anesthesia, the quaternary derivative of dimethylacetamide LKhT-12-02 has the greatest analgesic effect. The duration of the effect of the substance is over 3 hours. All the investigated compounds block sciatic nerve conduction. The longest effect is registered for LKhT-12-02.

Conclusions. Dimethylacetamide derivatives at concentrations of 0.5–1.0% exhibit a local anesthetic activity, and are effective for terminal, conduction and **infiltration** anesthesia. Their effect is due to blockade of nerve conduction.

Keywords

local anesthesia, dimethylacetamide compounds, terminal anesthesia, conduction, computational prediction, acute toxicity, isolated nerve.

Introduction

Over the past decades, revolutionary changes in clinical practice, the creation and widespread introduction of new high-tech methods of diagnosis and treatment make new demands for a modern drug for local anesthesia (Chitilian et al. 2016, Mennito 2016). Medical manipulations, which used to be impossible outside the hospital, have now become routine for outpatient surgery and invasive diagnostics (Mennito 2016).

The factor of the aging population, the extremely spread comorbidity, increasing requirements for drug safety, reduced cost of both a local anesthetic drug and medical equipment, as well as other resource costs associated with its use have great importance for the choice of a means and method of anesthesia at the present time (Forman 2010). Of particular importance when selecting a local anesthetic is the pharmacological characteristics, such as the rate of development of the effect, the depth of local anesthesia, the duration of action, and the speed of anesthesia recovery (Mennito 2016, Forman 2010).

Since its discovery and appearance in clinical practice, lidocaine has been the most common local anesthetic drug (Malamed 2007), which has assumed “the gold standard status” in dental and ophthalmic practices, as well as in outpatient surgery. However, a short duration of the drug action, a relatively wide range of its adverse effects made pharmacologists and clinicians search for more optimal medicinal solutions in this area.

At present, research in the field of pharmacology of local anesthetics is carried out in two main directions. The first, more traditional for pharmacologists, is related to the search for novel or chemically modified well-known molecules of medicinal substances. Great progress has been made in the stereopharmacology of bupivacaine, ropivacaine, etc. (Da Silva et al. 2017). However, it is becoming more important worldwide not just to develop novel effective molecules for a given type of local anesthesia, but rather to invent promising drug delivery systems (Riberio et al. 2017), which would allow, first, localizing the pharmacological effect at most, secondly, managing the profile of unwanted effects, and, finally, bringing the efficacy and safety of anesthetic relief to a qualitatively new level.

Recently, studies focusing on lidocaine (dimethylacetamide) derivatives have intensified in Russia. In a series of studies, their antiarrhythmic medication (Blinov and Kostin 2003; Blinov et al. 2014; Sernov et al. 2005) and the anti-ischemic (Kostin et al. 2003) activities were studied, and it was shown that the derivatives exceed their structural ancestor both by duration and by efficiency in experimental animals (Blinova et al. 2015) and in vitro (Balashov et al. 2005). All this served as the basis for assuming that this group of amino acid-substituted and quaternary derivatives of dimethylacetamide had a local anesthetic activity, which determined the relevance of this study.

Materials and methods

All the study protocols were reviewed and approved by the Local Ethics Committee of National Research Ogarev Mordovia State University (Minutes No. 10 of October 20, 2016).

Animals and biological materials

The experiments were performed on various laboratory animals and using biological material: 95 isolated sciatic nerves of *Rana radibunda* lake frog, 95 white rats of both sexes weighing 180–220 g, 265 SHK mice of both sexes weighing 18–22 g, 36 male guinea pigs (Agouti strain), and 18 male Soviet chinchilla rabbits. The laboratory animals were purchased in “Stolbovaya” and “Andreevka” Animal Breeding Facilities. The animals were maintained at the vivarium of National Research Ogarev Mordovia State University under conventional conditions, which met all the requirements of The National Standard of the Russian Federation “Principles of Good Laboratory Practice”.

Substances and drugs

The object of the study was tertiary derivatives of dimethylacetamide with an anion substituted with an amino or carboxylic acid residue, synthesized at The All-Union Scientific Center for the Safety of Biologically Active Substances at the Department of Chemistry and Technology of Synthetic Medications. Also, two quaternized systems, chemically derived from dimethylacetamide, were used as the object of the study. One of them contained the nitrogen atom in the aliphatic residue of the molecule, which was introduced into a cyclic structure (a compound under the laboratory code – LKhT-12-02). The other one was saturated with an additional radical with a covalent bond (a derivative under the laboratory code – LKhT-13-02). The physical and chemical characteristics of the tertiary substances are presented in Table 1.

All the compounds were studied as substances. Their solutions were prepared *ex tempore*, using twice-distilled water as a solvent. In all the models, the structural ancestor of the derivatives – lidocaine hydrochloride (Lidocaine Bufus by Renewal in plastic ampoules containing 2 ml of 10% solution, exp. date 11.2017, series 02354) was tested as a reference drug. In the study of the acute toxicity in case of subcutaneous administration and of a local anesthetic action on the terminal corneal anesthesia model, tetracaine hydrochloride was used as a reference drug (Tetracaine Hydrochloride Ophthalmic Solution USP 0.5% in 15 ml bottles, by Bousch and Lomb Pharmaceuticals, USA, exp. date 05.2018, series L47643). On the models of conduction anesthesia, bupivacaine hydrochloride (Bupivacaine Grindex by Grindex, Latvia, 5 mg/ml of bupivacaine monohydrate in 4 ml ampoules, series 15487, exp. date 12.2017) was used as a reference drug.

Table 1. Physical and Chemical Characteristics of Tertiary and Quaternary Derivatives of Dimethylacetamide

| No. | Laboratory code | Gross-formula of a derivative | Chemical name | M | Melting T, °C |
|-----|-----------------|-----------------------------------------------------------------|---------------------------------------------------------------------|--------|---------------|
| 1. | LKhT-3-00 | C ₁₉ H ₃₁ N ₃ O ₅ | L-Glutamate 2-Diethylamino-2',6'-Dimethylacetamide | 615.81 | 72–75 |
| 2. | LKhT -4-00 | C ₃₅ H ₅₅ N ₅ O ₇ | N-Acetyl-L-Glutamate 2- Diethylamino-2',6'-Dimethylacetamide | 657.83 | 80–83 |
| 3. | LKhT -5-00 | C ₁₆ H ₂₇ N ₃ O ₃ | Amino acetate 2- Diethylamino-2',6'-Dimethylacetamide | 309.41 | 74–76 |
| 4. | LKhT -6-00 | C ₁₈ H ₂₈ N ₂ O ₅ | Succinate 2- Diethylamino-2',6'-Dimethylacetamide | 352.42 | 120–122 |
| 5. | LKhT -2-01 | C ₁₉ H ₃₁ N ₃ O ₄ S | N-acetylcysteinate 2- Diethylamino-2',6'-Dimethylacetamide | 397.53 | 39–42 |
| 6. | LKhT-4-01 | C ₁₇ H ₂₉ N ₃ O ₃ | 2-amino propionate 2- Diethylamino-2',6'-Dimethylacetamide | 323.43 | 75–78 |
| 7. | LKhT -5-01 | C ₂₀ H ₃₆ N ₆ O ₃ | L-arginate 2- Diethylamino-2',6'-Dimethylacetamide | 408.55 | 80–83 |
| 8. | LKhT -6-01 | C ₂₃ H ₃₃ N ₃ O ₃ | β-Phenyl-α-amino propionate 2- Diethylamino-2',6'-Dimethylacetamide | 399.52 | 240–245 |

Reference drug solutions for terminal anesthesia were prepared immediately before use at the required concentration. In other models of anesthesia, the doses of the drugs were calculated basing on the available literature data concerning their acute toxicity index determined for subcutaneous administration. Also, based on the toxicological profile data, doses were calculated for dimethylacetamide derivatives. In case when toxicological studies and studies of local anesthetic effects were carried out in different specimen of animals, the dose conversion factors were used from (Freireich et al. 1966).

Experimental methods

The screening of activity and toxicity of the compounds was carried out by PASS (Prediction of Activity Spectra for Substances, version 9.1) computer-based method for predicting the biological activity of substances, based on analysis of training samples by Poroykov et al. (2000). The derivatives' acute toxicity when administered subcutaneously was investigated in accordance with international recommendations (Gad 2007). To study the local anesthetic activity of dimethylacetamide derivatives, a terminal anesthesia models of the rabbit eye cornea (Regnier 1982) and an [infiltration](#) anesthesia method in Agouti

guinea pigs (Bulbring and Wajda 1945) were used. The local anesthetic activity of the derivatives on the models of conduction anesthesia was determined by tail-flick test in mice and sciatic nerve blockade model in rats (Ouchi et al. 2013). The local irritant effect of the compounds was studied by Setnicar (1966). The impact of the studied compounds on the impulse conduction was studied in vitro experiments on frog isolated sciatic nerve specimens.

Statistical processing of the obtained results was carried out using conventional statistics methods by means of BioStat[®] software for Microsoft Windows, SPSS and PC iMac Retina (USA).

Results and discussion

The first stage of this study involved the pharmacological screening in the series of tertiary derivatives of dimethylacetamide and quaternized systems with a phenylacetamide base for the presence of local anesthetic activity in their spectrum. Using the PASS system, the probability of presence (*Pa*) and absence (*Pi*) of pharmacological activity was evaluated (the maximum probability is 1) in the series of the substances. Figure 1 represents the obtained results. The computerized prediction showed that two

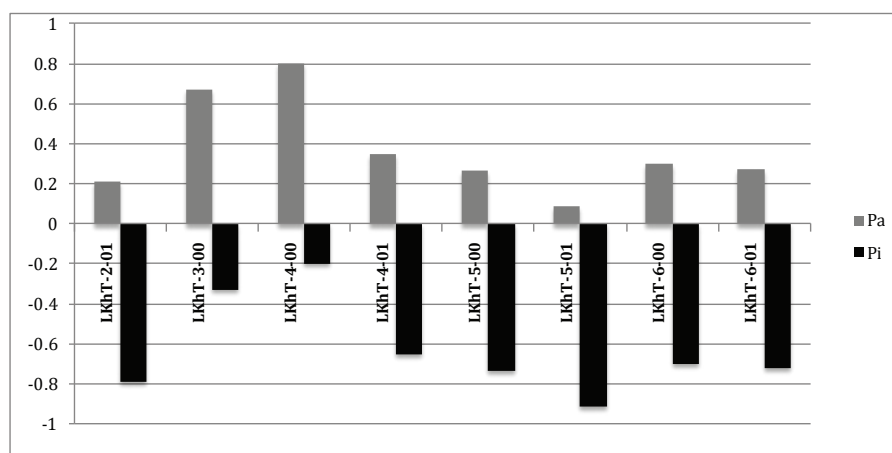


Figure 1. Computational probability of presence (*Pa*) or absence (*Pi*) of local anesthetic property in the series of dimethylacetamide derivatives

substances from the group of tertiary amino acid-substituted derivatives are highly likely to have a local anesthetic effect: a probability of this effect for LKhT-4-00 derivative with N-acetyl-L-glutamic acid as anion was the largest among others in the series, with Pa being 0.801. The tertiary derivative LKhT-3-00 with L-glutamic acid residue is somewhat inferior to the predicted activity, with Pa being 0.669. Among the quaternized systems, only LKhT-12-02 had a local anesthetic property (Pa is 0.528). So the aforementioned derivatives with high anesthetic potency were selected for further investigation.

Since one of the important practical issues was to compare the range of therapeutic effect of the compounds with that of their structural analogs and other reference drugs, acute toxicity of dimethylacetamide derivatives was studied through subcutaneous administration to rodents. The results of the study are shown in Figure 2.

In all cases, the replacement of the hydrochloride anion in lidocaine structure with the amino acid residue reduced the molecule toxic profile. At the same time, the DL_{50} index of the compounds changed in the ascending order as follows: lidocaine (236 ± 7 mg/kg), its tertiary derivatives with N-acetyl-L-glutamic acids residue (LKhT-4-00 – 297 ± 8 mg/kg) and L-glutamic acids residue (LKhT-3-00 – 303 ± 14 mg/kg). Different data on acute toxicity was obtained for the quaternary derivative LKhT-12-02 when administered subcutaneously. The DL_{50} index of the compound was 118 ± 4 mg/kg. In general, all studied compounds belonged to class 3 (moderately toxic) of substances toxic and danger when administered subcutaneously.

The local anesthetic activity of the most promising tertiary and quaternary derivatives of dimethylacetamide on the terminal anesthesia model was studied at 0.5, 1.0, and 2.0% solution concentrations. The latent period of the anesthesia onset and its duration were determined. Regnier index and EC_{30} were calculated. Simultaneously, a local irritant effect of the substances was recorded. Both of the investigated tertiary compounds are significantly inferior in strength and duration of activity to tetracaine at all studied concentrations. However, when comparing with a structural analogue, it was found that LKhT-3-00 and LKhT-4-00 exceeded lidocaine in local painkilling action. Thus, with a similar latent period of anesthesia onset, Regnier index values of lidocaine at 2.0 – 1.0 – 0.5% concentrations were 315 – 149 – 53, the index values of LKhT-3-00 at the same concentrations were 456 – 234 – 85, and index values of substance LKhT-4-00 were 514 – 304 – 107. Such Regnier index values made it possible to suggest that the tertiary derivatives of dimethylacetamide caused deeper terminal anesthesia. The duration of the effect of the compounds also differed from that of lidocaine. LKhT-4-00 exceeded lidocaine at all concentrations, whilst the substance under the laboratory code LKhT-3-00 induced more continuous anesthesia only at the top 2% concentration. EC_{30} values of LKhT-3-00 and LKhT-4-00 compounds were 1.78 and 1.47, respectively.

The pharmacological characteristics of the effect of the quaternary derivative of LKhT-12-02 on this model were somewhat different. Being compared with all the reference drugs and tertiary compounds of lidocaine, the latent

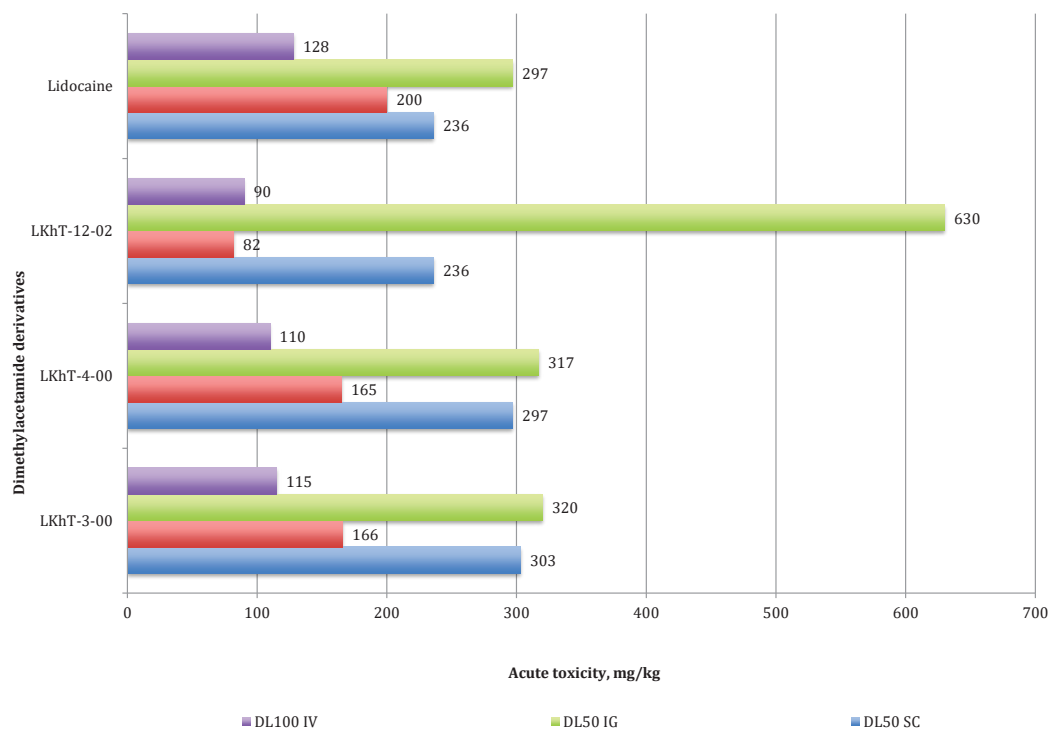


Figure 2. Index values (Mean) of dimethylacetamide derivatives DL_{50} (DL_{100} for IV administration) for different administration routes (mg/kg). Note: IV – intravenous, IG – intragastric, SC – subcutaneous

period of anesthesia onset induced by LKhT-12-02 significantly increased: when the solution was instilled at a concentration of 0.5%, it averaged 17 minutes. The analgesic effect developed at the fastest rate, within 13 min after instillation when the substance was administered at a maximum 2% concentration. The depth of anesthesia was also incomparably low in comparison with that reached when administering the reference drugs. The obtained data were not enough to calculate the value of EC_{30} index, only with a certain approximation its value was possible to estimate at the level of 11.56.

Based on the results of the terminal anesthesia model of rabbit eye cornea and the data on acute toxicity of the compounds administered subcutaneously, the range of the compounds' therapeutic effect was calculated. The results of the calculations are shown in Figure 3.

The lowest value of the index was estimated for the quaternary derivative of dimethylacetamide LKhT-12-02, which was due to a rather high toxicity and low pharmacological activity of the compound. From the authors' point of view, the tertiary derivatives of lidocaine – LKhT-4-00 and LKhT-3-00 compounds – had an optimal range of safe concentrations, which made it possible to consider them as potential drugs for applying in this type of anesthesia.

To assess the pharmacological activity of dimethylacetamide derivatives on the infiltration anesthesia model, the Bulbring and Wajda method was used. Each compound was evaluated at three concentrations: 0.25, 0.5, and 1.0%. The indices of infiltration anesthesia and

relative local anesthetic activity were assessed (Fig. 4). The tertiary derivatives of dimethylacetamide exhibited local anesthetic properties on this model. LKhT-3-00 and LKhT-4-00 compounds at higher concentrations caused complete anesthesia.

In this case, the local anesthetic activity of LKhT-3-00 substance at 1.0% concentration was inferior to that of lidocaine, whereas the derivative with N-acetyl-L-glutamic acid as an anion (LKhT-4-00) was superior to the reference drug by the depth of anesthesia at 0.5% concentration. The quaternary compound LKhT-12-02 on this anesthesia model demonstrated no discernible pharmacological activity. The studied dynamics of the relative local anesthetic activity of lidocaine and of the compounds under study was dose-dependent: the depth of anesthesia increased with increasing concentration of the administered solution. However, it should be emphasized that lidocaine curve was more linear, while the derivatives' curves had an exponential form, which indicated that these substances reached the threshold concentration at 0.4-0.6% level.

LKhT-3-00 and LKhT-4-00 demonstrated a high activity on the models of conduction anesthesia of mice tail and rat sciatic nerve. In the most concentrated solutions, the substances caused nerve conduction blockade comparable in depth with reference drug bupivacaine hydrochloride. The duration of the compounds' effect when compared to that of lidocaine was significantly higher. The quaternary derivative LKhT-12-02 showed encouraging results on these models. After administering the compound, upon

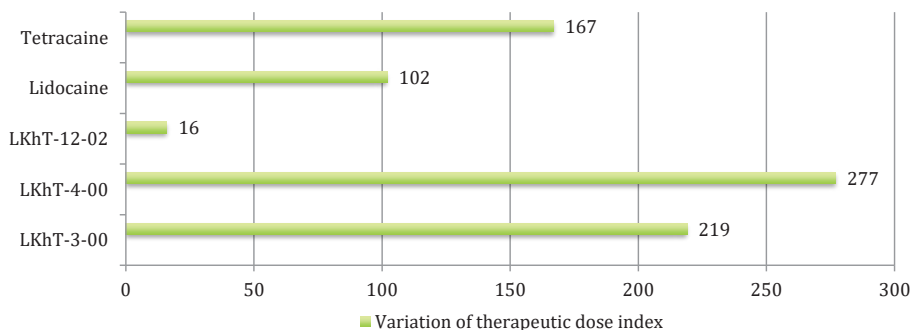


Figure 3. Range of therapeutic doses index for dimethylacetamide derivatives calculated on rabbit cornea anesthesia model

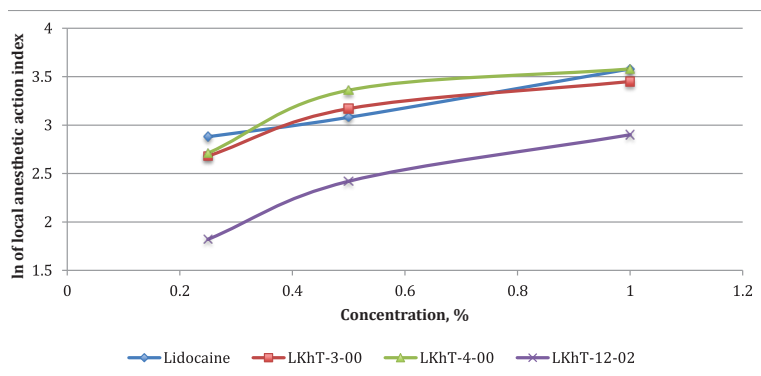


Figure 4. Curves of the derivatives' relative local anesthetic action calculated on the model of infiltration anesthesia

a latent period of 18 to 26 minutes, a deep and prolonged blockade followed, comparable with that after administering bupivacaine. Moreover, the duration of the pharmacological effect was 180 minutes. Figure 5 shows the ratios of the EC_{50} values calculated for the substances on models of conduction anesthesia in mice and rats.

From the data presented, it was clearly seen that EC_{50} values for LKhT-3-00 and LKhT-4-00, as well as for LKhT-12-02 substance, obtained on different models of conduction anesthesia were very close to each other. At the same time, the most active compound on these models was derivative LKhT-12-02, despite the long latent period of the anesthesia onset.

In the experiments on isolated sciatic nerve specimens of the lake frog, the effect of dimethylacetamide derivatives on action potential amplitude and A-fibers conduction was studied. The test substances suppressed both the tonic and rhythmic components of the conduction process. However, the relaxation time of volt-ampere profile of a nerve perfused by LKhT-12-02 was much slower and in contrast to lidocaine and its tertiary derivative LKhT-4-00 lasted several hours (Fig. 6).

Thus, dimethylacetamide derivatives exhibited properties of local anesthetics effective for terminal, conduction and infiltration anesthetics.

Conclusions

According to the obtained data, the following conclusions were made:

1. Computer prediction of the presence of tertiary and quaternary (allyl and allylmorpholine) derivatives of dimethylacetamide in the therapeutic spectrum made it possible to select the compounds that were promising for further experimental studies: a compound with L-glutamic acid residue (LKhT-3-00, Pa 0.669), a compound with N-acetyl-L-glutamic acid (LKhTT-4-00, Pa 0.801) and a quaternary derivative LKhT-12-02 (Pa 0.528).
2. Acute toxicity of tertiary derivatives of dimethylacetamide LKhT-3-00 and LKhT-4-00 when administered subcutaneously to mice was lower than that of the structural analog lidocaine, while the quaternary compound was more toxic than lidocaine when using this route of administration.
3. LKhT-3-00 and LKhT-4-00 had a local anesthetic activity on models of infiltration, terminal and conduction anesthetics, exceeding lidocaine in duration and depth of analgesic effect at 0.5-1% concentrations. LKhT-4-00 compound had the widest range of therapeutic do-

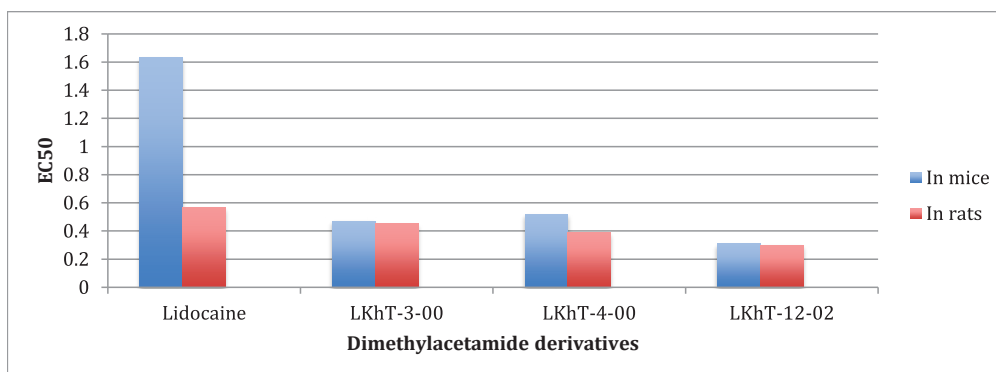


Figure 5. EC_{50} indices calculated for the derivatives on models of conduction anesthesia in mice and rats

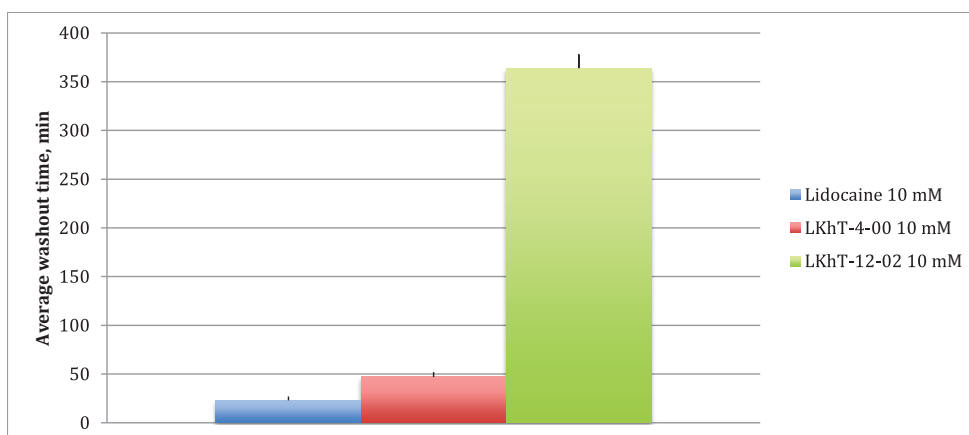


Figure 6. Average washout time of ($M \pm SD$) the test substances at a concentration of 10 mM when stimulating the isolated sciatic nerve

ses. The compounds did not cause a locally irritating effect on rabbit eye tissue.

4. N-allyl-N-(2,6-dimethylphenylaminocarbonylmethyl)morpholinium bromide (LkHT-12-02) compound had no analgesic effect on the models of terminal and infiltration anesthetics, but it induced a deep block of conduction over a mixed nerve lasting more than 3 hours. A specific pharmacological effect of the substance was a long latent period of an analgesic effect onset.

References

- Balashov VP, Blinov DS, Kazachenko VN, Astashev ME, Agenosova OG (2005) Membrane mechanisms of antiarrhythmic action of quaternidine. *Bulletin of Experimental Medicine and Biology [Byulleten eksperimentalnoy meditsiny i biologii]* 139(6): 688–691. <https://doi.org/10.1007/s10517-005-0379-y> [In Russian]
- Blinov DS, Kostin YaV (2003) Study of an antiarrhythmic action of tertiary derivative of lidocaine. *Russian Cardiological Journal [Rossiyskii Kardiologicheskii Zhurnal]* 6: 56–58. [In Russian]
- Blinov DS, Singh LN, Elizarova JN, Blinova EV, Skachilova SYa, Salamova EI, Meleshkin AI (2014) Comparative study of toxicity and antiarrhythmic activity of some organic compounds of dimethylacetamide. *Experimental and Clinical Pharmacology [Eksperimentalnaya i klinicheskaya farmakologiya]* 77(5): 20–22. [In Russian]
- Blinova EV, Skachilova SYa, Blinov DS, Singh LN, Elizarova JN, Meleshkin AI, Ivanova EA, Salamova EI (2015) Comparative study of toxicity and antiarrhythmic activity of novel N-substituted benzamide derivative. *Bulletin of New Medical Technology [Vestnik novykh meditsinskikh tekhnologii]* 22(1): 15–18. [In Russian]
- Bulbring E, Wajda I (1945) Biological comparison of local anaesthetics. *The Journal of Pharmacology and Experimental Therapeutics* 85: 78–84. [PubMed]
- Chitilian HV, Eckenhoff RG, Raines DE (2016) Anesthetic drug development: Novel drugs and new approaches. *Surgical Neurology International* 4(1): 2–10. <https://doi.org/10.4103/2152-7806.109179> [PubMed] [PMC]
- Da Silva GR, Riberio LNM, Mitsutake H, de Paula E (2017) Optimised NLC: a nanotechnological approach to improve the anesthetic effect of bupivacaine. *International Journal of Pharmaceutics* 529(1–2): 253–263. <https://doi.org/10.1016/j.ijpharm.2017.06.066> [PubMed]
- Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE (1966) Quantitative comparison of toxicity of anticancer agents in mouse, rat, guinea pig, rabbit, cat, dog, monkey and man. *Cancer Chemotherapy Reports* 50(4): 219–244. [PubMed]
- Forman SA (2010) Molecular approaches to improving anesthetics. *Anesthesiology Clinics of North America* 28(4): 761–771. <https://doi.org/10.1016/j.anclin.2010.08.004> [PubMed] [PMC]
- Gad CS (2007) *Animal Models in Toxicology* (2nd edn). Taylor and Francis, New York, 950 pp.
- Kostin YaV, Blinov DS, Moiseeva IYa (2003) Antiarrhythmic action of ammonium derivative of trimecaine under the condition of ischemic heart injury. *Experimental and Clinical Pharmacology [Eksperimentalnaya i klinicheskaya farmakologiya]* 66(5): 2–31. (In Russian)
- Malamed SF (2007) Articaine versus lidocaine: the author responds. *Journal of the California Dental Association* 35(6): 383–385. [PubMed]
- Mennito AS (2016) Local anesthetics review. *ADA CERP*: 287.
- Ouchi K, Sekine J, Koga Y, et al. (2013) Establishment of an animal model of epidural anesthesia and sedative tail-flick test for evaluating local anesthetic effects in rats. *Experimental Animals* 62(2): 137–144. <https://doi.org/10.1538/expanim.62.137> [PubMed]
- Poroikov VV, Filimonov DA, Borodina YV, Lagunin AA, Kos A (2000) Robustness of biological activity spectra predicting by computer program PASS for noncongeneric sets of chemical compounds. *Journal of Chemical Information and Computer Sciences* 40(6): 1349–1355. <https://doi.org/10.1021/ci000383k> [PubMed]
- Regnier A (1982) Effet de la sédation par la xylazine, l'acépromazine et la kétamine sur l'hémogramme du chat. *Revue de Médecine Vétérinaire* 133: 243–248. [in French]
- Riberio LNM, Breikreitz MC, Guilherme V, da Silva GHR, Couto VM, Castro SR, de Paula BO, Machado D, de Paula E (2017) Natural lipids-based NLC containing lidocaine: from pre-formulation to in vivo studies. *European Journal of Pharmaceutical Sciences* 106: 102–112. <https://doi.org/10.1016/j.ejps.2017.05.060> [PubMed]
- Sernov LN, Skachilova SYa, Druzhinina VV, Shilova EV, Blinov DS, Kostin YaV (2005) 2-diethylamino-2',6'-dimethylphenylacetamide derivatives with antiarrhythmic activity. *Journal of Chemistry and Pharmaceuticals [Khimiko-farmatsevticheskii zhurnal]* 39(7): 350–353. [In Russian]
- Setnicar I (1966) Tolerance indices of some phenoxyethylamino derivatives with local anaesthetic properties. *Arzneimittel-Forschung* 16(5): 623. [PubMed]

Acknowledgements

The authors are extremely grateful for providing the test substances to Russian State Prize Holder Prof. S.Ya. Skachilova, who supervised their synthesis.

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