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STUDY OF ANALGESIC AND MYOTROPIC SPASMOLYTIC ACTIVITY OF ALKYLCARB

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The work is devoted to the search for new biologically active substances in a series of alkylamides of dihydroquinoline-3-carboxylic acid. Analgesic properties of 30 newly synthesized substances were studied, which made it possible to identify the leader compound (provisional name alkylcarb) and recommend its effectiveness for further research as an antispasmodic agent for pain relief. It has been established experimentally, that the substance alkylcarb exhibits concentration-dependent vasodilatory properties in vitro on segments of the thoracic aorta of rats. The data, obtained in the work, justify the prospect of using the leader substance as a new analgesic and antispasmodic drug. The research expands and deepens knowledge about the pharmacological properties of alkylamide derivatives of dihydroquinoline-3-carboxylic acid.

The aim *of the work was to conduct screening studies to establish the analgesic activity of a newly synthesized series of chemical compounds among alkylamides of dihydroquinoline-3-carboxylic acid and to study the myotropic spasmolytic activity of the leader substance.*

Materials and methods. *Analgesic properties of alkylamides of dihydroquinoline-3-carboxylic acid were studied on outbred white mice in the "acetic acid convulsions" test. During the experiment, the animals were treated in accordance with the International Principles of the European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes (Strasbourg, March 18, 1986). The studied substances were administered intragastrically to experimental animals at a dose of 10 mg/kg in the form of a finely dispersed aqueous suspension, stabilized with Tween-80. Voltaren at a dose of 8 mg/kg, recommended for preclinical studies, and analgin at a dose of 50 mg/kg were chosen as reference drugs.*

The studies of the contractile activity of smooth muscle vessels were carried out on segments of the thoracic aorta of rats of both sexes weighing 180-200 g. The studies of dilator reactions were carried out against the background of preliminary contraction with phenylephrine at a concentration of 10^{-6} *mol/l. The antispasmodic efficiency of the new compound was determined in comparison with the classic antispasmodic drotaverine.*

The statistical processing of the results was carried out using the package of statistical analysis of electronic spreadsheets Exel, with the help of the program "Statgraphics Plus v. 3.0." and the standard package of statistical programs "Statistica, V. 6.0". We used the Student's test, a non-parametric analog of univariate variance analysis - the Kruskal-Wallis test, and the Mann-Whitney test. Differences were considered statistically significant at $p<0.05$.

Results. *The study of the analgesic activity of substances* AO_1-AO_{30} *in the "acetic acid convulsion" test in mice showed that a compound* AO_{26} *(provisional name alkylcarb) has the most pronounced analgesic activity when administered intragastrically. In the "acetic acid convulsion" test, alkylcarb (10 mg/kg, per os) probably reduces the number of convulsions, caused by acetic acid. The level of activity of this compound is comparable to the activity of diclofenac (8 mg/kg, per os) and exceeds analgin (50 mg/kg, per os). The substance alkylcarb relieved vasospasm at the level of the comparison drug drotaverine in in vitro experiments on a model of an isolated fragment of the thoracic aorta of rats against the background of previous constriction with phenylephrine.*

Conclusion. *Today, the search for new highly effective non-opioid analgesics is an urgent problem of modern pharmacology, since painkillers used in clinical practice do not meet the requirements of efficiency and safety. In this regard, in recent years, scientists of the National Pharmaceutical University have been intensively searching for new, highly effective substances with antinociceptive, anti-inflammatory and antipyretic effects among alkylamides of dihydroquinoline-3-carboxylic acid.*

Keywords: *alkylamides of dihydroquinoline-3-carboxylic acid, non-narcotic analgesics, antispasmodics, alkylcarb.*

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the widely used pharmacological groups in pain therapy. Inflammation and pain are the most frequent symptoms of various diseases and represent an important clinical problem [1]. In connection with the polyetiological nature and peculiarities of the mechanisms of the development of the inflammatory process and pain syndrome, drugs of various pharmacological groups of narcotic and non-narcotic analgesics (NNAs) and NSAIDs are used for the treatment of many acute and chronic diseases [2].

In order to determine the structure of the market of drugs, used for pain relief, we analyzed the assortment of NSAIDs, which according to the ATC classification belong to the group N02B Other analgesics and antipyretics and are the largest group among analgesics.

According to the State Register of Drugs of Ukraine as of June 1, 2023, this group includes 313 names of drugs from four subgroups of the fourth level of classification. The most numerous is the group N02BE Anilides, which is represented by 230 drugs from subgroups N02BE01 Paracetamol and N02B E51 Paracetamol, combinations excl. psycholeptics. The second largest number of registered drugs is the group N02BB Pyrazolones – 42 drugs from subgroups N02BB02 Metamizole sodium, N02BB52 Metamizole sodium, combinations excl. psycholeptics, N02BB72 Metamizole sodium, combinations with psycholeptics and N02BB74 Propyphenazone, combinations with psycholeptics. The group N02BA Salicylic acid and derivatives is represented by two subgroups (N02BA01 Acetylsalicylic acid and N02BA51 Acetylsalicylic acid, combinations excl. psycholeptics) with a total of 37 drug names. The smallest group is N02BG Other analgesics and antipyretics, which includes only 4 names of drugs (subgroup N02BG06 Nefopam) [3].

Fig. 1 shows the general ratio of subgroups of the N02B group by the number of registered drugs.

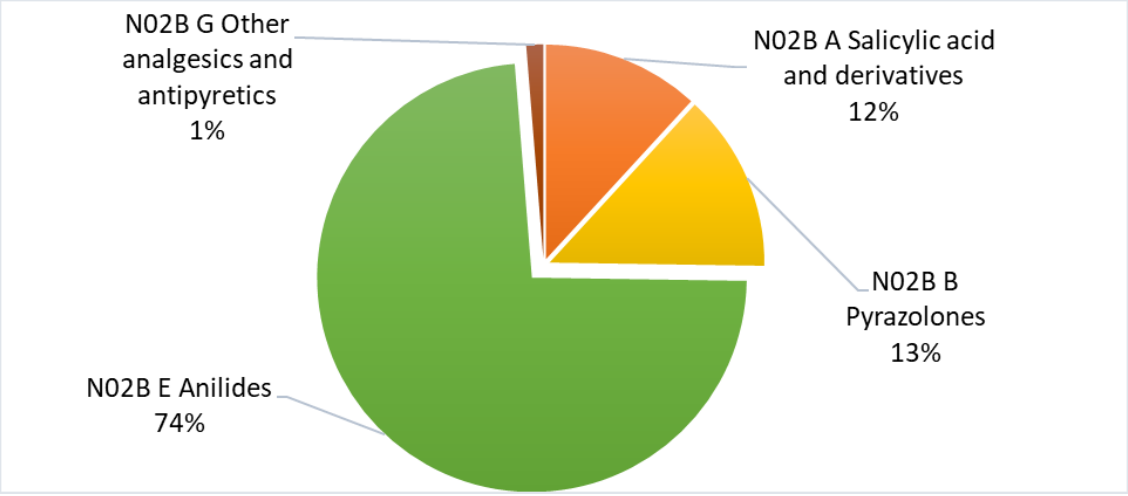

Fig. 1. Structure of the group N02B Other analgesics and antipyretics by the number of registered drugs without taking into account the dosage form

The analysis of the geographical representation of manufacturers showed that the pharmaceutical products of the analyzed group are supplied by manufacturers from 21 countries. The total share of drugs of Ukrainian manufacturers is 47.6 % of the registered assortment. The second largest number of drugs of the analgesic group, presented in Ukraine, is India with a share of 17.9 %, the third largest number of drugs is France (7.7 % of the assortment of the group N02B Other analgesics and antipyretics). Other producing countries are represented by less than 5 % of the assortment of drugs of the group.

According to the results of the analysis of the geographical distribution of manufacturers in the subgroups, it has been established, that the vast majority of drugs with the active substance acetylsalicylic acid are produced by domestic companies – the share of such drugs in the subgroups is almost 70 % in each of the N02BA subgroups.

Drugs of the N02BB Pyrazolones group are also mainly represented by Ukrainian manufacturing companies.

The N02BE Anilides group, which is the largest in terms of number of drugs, includes drugs from 19 countries: the assortment of the subgroup N02BE01 Paracetamol is formed mainly of drugs of Ukrainian production (56 % of drugs of the subgroup among 10 producing countries), and the assortment of the subgroup N02BE51 Paracetamol, combinations excl. psycholeptics – of drugs of Indian production (30 % of drugs of the subgroup among 17 producing countries).

The smallest group N02BG Other analgesics and antipyretics, formed by drugs with the active substance nefopam, is represented on the Ukrainian market by manufacturers from Ukraine (50 % of the assortment), Greece and France (25 %, respectively).

The general distribution of drug-producing countries by group is shown in Fig. 2.

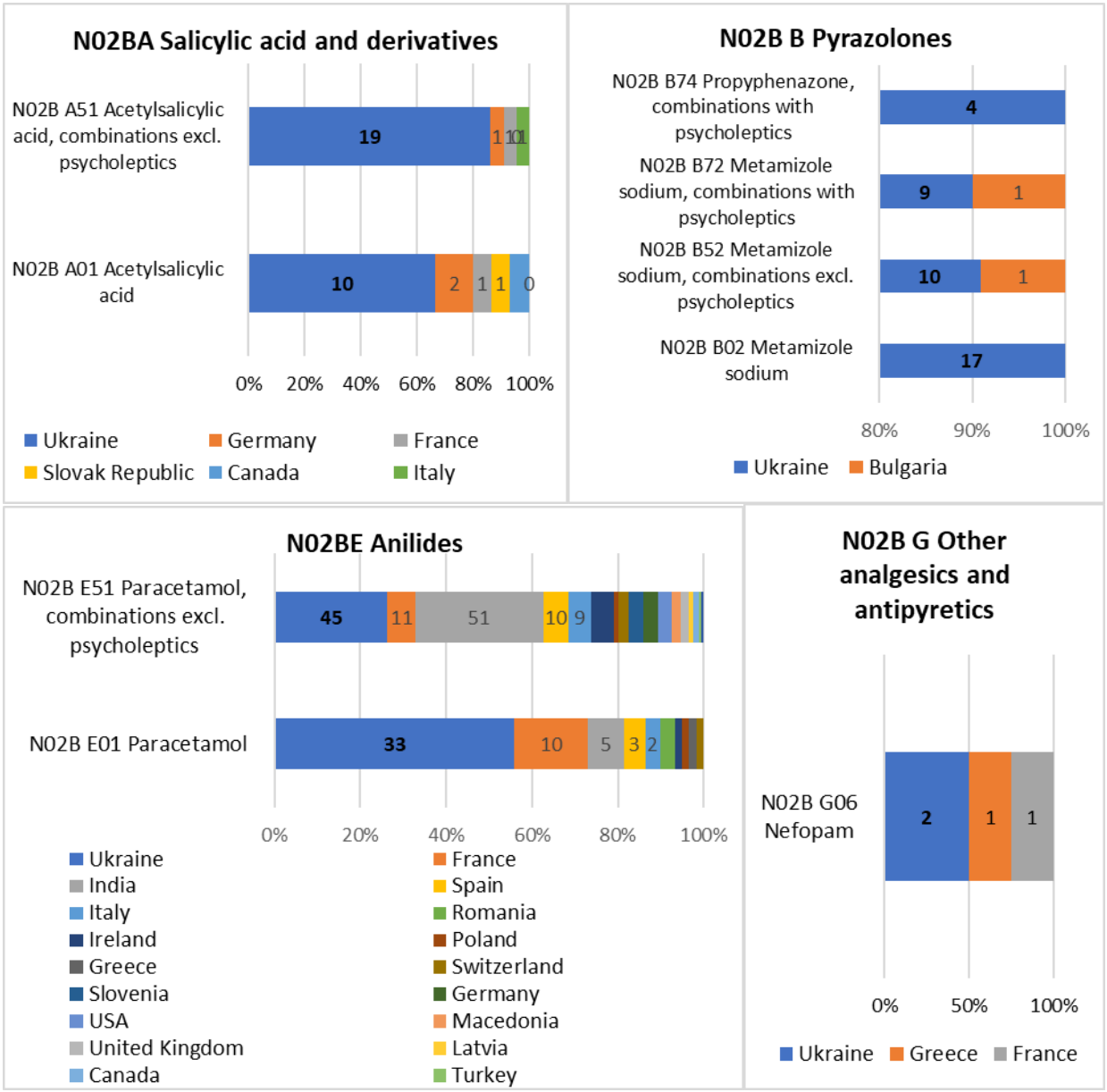

Fig. 2. Geographical distribution of manufacturers of drugs of the group N02B Other analgesics and antipyretics by the number of drugs, presented on the market of Ukraine

At the next stage, we analyzed the assortment of registered drugs of the group N02B Other analgesics and antipyretics group by release forms (Fig. 3). It has been determined, that there are 12 pharmaceutical forms in total, and the most numerous are drugs in solid forms - tablets, powders. Thus, the tablets segment includes 136 drugs or 43.5 % of the assortment, among which the vast majority are in the subgroup N02BE51 Paracetamol, combinations excl. psycholeptics (53 names of drugs in the form of tablets and 2 names of drugs in the form of effervescent tablets). Powders for oral solutions account for 111 names of drugs or 35.5 % of the assortment and are also represented only in the subgroup N02BE51 Paracetamol, combinations excl. Psycholeptics [4].

Among the liquid dosage forms, there are more solutions for injection – 25 names of drugs or 8 % of the assortment of the group N02B, which were distributed as follows among subgroups: N02BE01 Paracetamol – 16 names of drugs, N02BB02 Metamizole sodium – 5 names of drugs and N02BG06 Nefopam – 4 names.

It is necessary to note a small number of names of drugs in the form of syrups, intended for the treatment of children – 5 drugs containing paracetamol. The rest of the children's dosages of drugs of the group N02B Other analgesics and antipyretics are represented by suppositories.

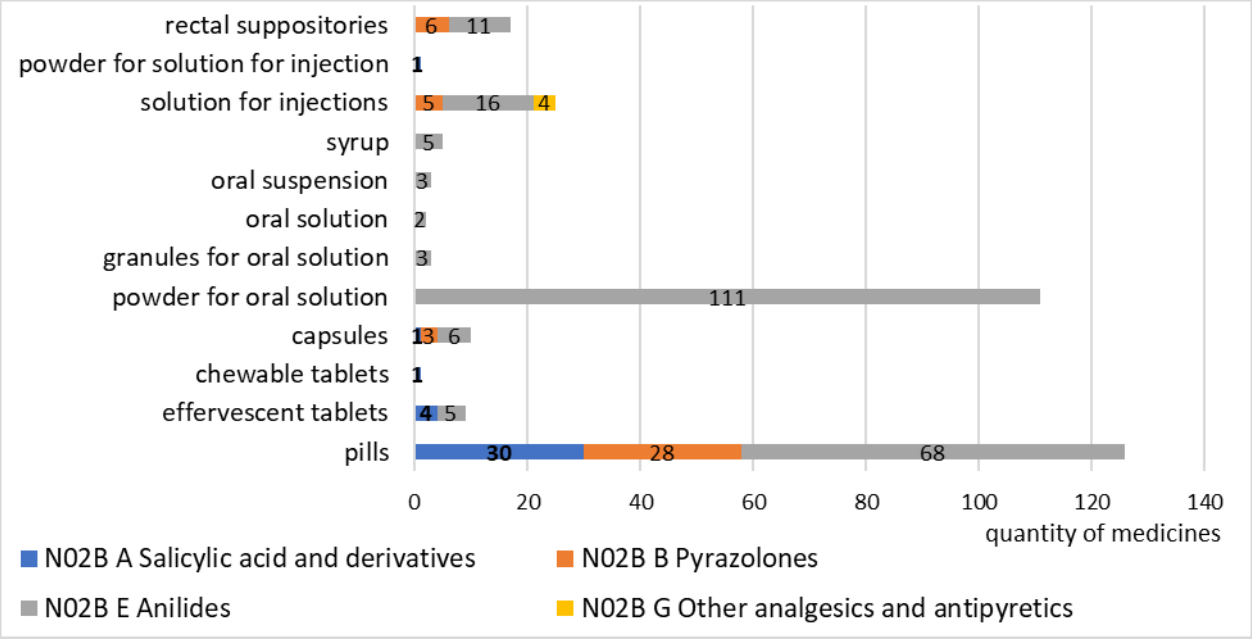

Fig. 3. Structure of the assortment of the group N02B Other analgesics and antipyretics by the forms of drug release

Thus, the conducted analysis indicates a sufficiently wide range of drugs of the group N02B Other analgesics and antipyretics group with different active substances, in dosage forms and by producing countries, which allows meeting the needs of the majority of patients who require pain relief from the use of non-narcotic analgesics.

At the same time, the relevance of the problem is determined not only by the prevalence of diseases that are accompanied by pain syndrome, but also by the frequency of adverse reactions that occur when using anti-inflammatory and analgesic drugs [5]. The use of drugs from the group of NNAs and NSAIDs is often accompanied by the development of such side effects as hepatotoxicity, nephrotoxicity, gastrotoxicity, acid-base imbalance, and others, which are associated with the peculiarities of their mechanism of action [6]. In addition, a significant arsenal of modern NNAs and NSAIDs and the creation of new selective COX-2 inhibitors do not solve the problem of side effects with long-term use of drugs of this group in the clinic. However, despite the high frequency and severity of complications, NNAs and NSAIDs continue to be the most common drugs [7].

Thus, the search for new highly effective non-opioid analgesics is an urgent problem of modern pharmacology, since the painkillers used in clinical practice do not meet the requirements of efficiency and safety. In this regard, in recent years, scientists of the National Pharmaceutical University have been intensively searching for new, highly effective substances with antinociceptive, anti-inflammatory and antipyretic effects among alkylamides of dihydroquinoline-3-carboxylic acid [8, 9]. The purpose of this series of studies was to conduct a screening to establish the analgesic activity of a newly synthesized series of chemical compounds among alkylamides of dihydroquinoline-3-carboxylic acid and to study the myotropic spasmolytic activity of the leader substance.

2. Materials and methods

The objects of the research were 30 original compounds - alkylamide derivatives of dihydroquinoline-3-carboxylic acid (Fig. 4). The substances were obtained by targeted synthesis at the Department of Pharmaceutical Chemistry of the National Academy of Sciences under the supervision of Doctor of Chemical Sciences, Professor I.V. Ukrainets. The obtained compounds are white and cream crystalline substances with distinct melting points, soluble in ethanol and dioxane and insoluble in water. Their structure was confirmed by the methods of elemental analysis and IR spectroscopy, and their purity was confirmed by thin-layer chromatography.

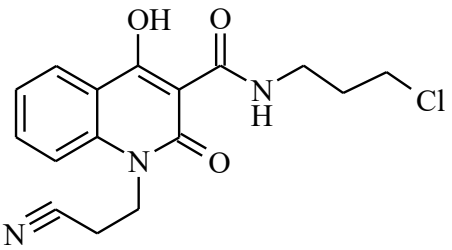

Fig. 4. General structural formula of alkylamides of dihydroquinoline-3-carboxylic acid

The research was conducted in 2017–2018.

Analgesic properties of alkylamides of dihydroquinoline-3-carboxylic acid were studied on outbred white mice in the "acetic acid convulsions" test [10]. During the experiment, the animals were treated in accordance with the International Principles of the European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes (Strasbourg, March 18, 1986). The studied substances were administered intragastrically to experimental animals at a dose of 10 mg/kg in the form of a finely dispersed aqueous suspension, stabilized with Tween-80. Since a fairly large number of new compounds were studied, it did not allow conducting the experiment in 1

day, a new group of control pathology was introduced for every 5 substances during the experiment. Voltaren (Novartis, 25 mg diclofenac sodium, series 0544), which was administered to mice intragastrically once at a dose of 8 mg/kg, recommended for preclinical studies, and analgin (Darnytsia, 500 mg, series 0348), received intragastrically once at a dose of 50 mg/kg, were selected as reference drugs. The research was conducted on animals that were kept in the vivarium of the Central Research Laboratory of the National Pharmaceutical University on a regular food and water diet.

The studies on the determination of myotropic antispasmodic activity were conducted at the Department of Pharmacology and Clinical Pharmacology of the Dnipro State Medical University of the Ministry of Health of Ukraine under the supervision of Doctor of Medicine, Prof. O. O. Nefyodov The study of the contractile activity of smooth muscle vessels was carried out on segments of the thoracic aorta of rats of both sexes weighing 180-200 g. The animals were removed from the experiment by cervical dislocation. Taking into account the fact that the rat aorta in its initial state has an insufficiently pronounced basal tone, studies of dilator reactions were carried out against the background of previous contraction with phenylephrine at a concentration of 10^{-6} mol/l. The obtained level of tone was taken as the initial level and all vascular reactions changed relative to the given level of isometric tension of smooth muscle cells. The strength, with which the contractile response, caused by phenylephrine, was suppressed, was considered the registered reaction of the test object. The studied drugs in an increasing concentration in the range from 10^{-10}-10^{-2} in a standard solution with the addition of phenylephrine were placed in variable containers, from where they were fed directly into the working chamber by a peristaltic pump at a flow rate of 1.5 ml/min. The necessary concentration in the working chamber was established within 1–2 seconds. The spent solution was pumped out by a second peristaltic pump with a similar flow rate. A series of successive concentrations (10^{-10}–10^{-2}) for each drug was used to construct dose-effect curves. The duration of exposure for each of the concentrations was 3-5 minutes. The area under the curves of equal segments of the registration of contractile activity for each of the concentrations was compared as a criterion for the activity of the thoracic aorta [11]. The antispasmodic efficiency of the new compound was determined in comparison with the classical antispasmodic drotaverine (Darnytsia, 40 mg, series 0844).

The statistical processing of the results was carried out using the package of statistical analysis of electronic spreadsheets Ecxel, with the help of the program "Statgraphics Plus v. 3.0." and the standard package of statistical programs "Statistica, V. 6.0" [12]. We used the Student's test, a non-parametric analog of univariate variance analysis – the Kruskal-Wallis test, and the Mann-Whitney test. Differences were considered statistically significant at $p<0.05$ [13].

3. Research results

The results of the study of the analgesic properties of alkylamides of dihydroquinoline-3-carboxylic acid are shown in Table 1.

Table 1

Analgesic activity of alkylamide derivatives of dihydroquinoline-3-carboxylic acid (AO_1–AO_{30}), voltaren and analgin in the "acetic acid convulsion" test in mice, (M±m), n=6

Conditions of the experiment (group, code of a compound)	Dosage, mg/kg	Number of vessels, M±m	Analgesic activity, %
1	2	3	4
AO_1	10	55.6±1.48	15.2
AO_2	10	50.1±1.52*	23.6
AO_3	10	48.6±1.43*	25.9
AO_4	10	37.2±1.12*	43.3
AO_5	10	50.1±1.38*	23.6
Control pathology	–	65.6±1.88	–
AO_6	10	45.6±1.41*	28.1
AO_7	10	50.9±1.49*	19.7
AO_8	10	40.8±1.47*	35.6
AO_9	10	38.6±1.49*	39.1
AO_{10}	10	52.6±1.35*	17.0
Control pathology	–	63.4±1.82	–
AO_{11}	10	44.6±1.29*	32.5
AO_{12}	10	45.5±1.44*	31.2
AO_{13}	10	52.9±1.49*	20.0
AO_{14}	10	48.6±1.47*	26.5
AO_{15}	10	54.3±1.44*	17.9
Control pathology	–	66.1±1.87	–
AO_{16}	10	45.6±1.45*	26.3
AO_{17}	10	43.1±1.42*	30.4
AO_{18}	10	45.6±1.40*	26.3
AO_{19}	10	49.6±1.47*	19.9

Continuation of the Table 4

1	2	3	4
AO_{20}	10	57.6±1.55	6.9
Control pathology	–	61.9±1.59	–
AO_{21}	10	46.4±1.44*	23.7
AO_{22}	10	48.6±1.47*	20.1
AO_{23}	10	40.3±1.40*	33.7
AO_{24}	10	52.8±1.49	13.2
AO_{25}	10	51.6±1.43	15.1
Control pathology	–	60.8±1.51	–
AO_{26}	10	31.6±1.12*/ α	51.6
AO_{27}	10	45.4±1.52*	30.5
AO_{28}	10	50.4±1.52*	22.8
AO_{29}	10	51.3±1.52*	21.4
AO_{30}	10	43.8±1.52*	32.9
Voltaren	8	33.4±1.52*	48.8
Analgin	50	35.9±1.52*	45.0
Control pathology	–	65.3±1.76**/ α	–

*Note: * – the difference is significant relative to the control pathology group, p<0.05; ** – the difference is significant relative to voltaren, p<0.05; α – the difference is significant relative to analgin, p<0.05; n – number of animals in the group*

The experimental model of "acetic acid convulsions" allows to study the mechanism of peripheral analgesic action of new substances. The pathogenesis of this experimental model is based on chemical pain irritation. Intraperitoneal administration of acetic acid solution induces general activation of the nociceptive system and promotes local release of histamine, bradykinin, serotonin, prostaglandins, and leukotrienes. This leads to the development of involuntary contractions of the abdominal muscles of laboratory animals – "convulsions", accompanied by arching of the back and stretching of the animal's hind limbs [14].

As can be seen from Table 1, the number of "convulsions" in the animals of the control pathology groups ranged from 60.8±1.51 to 66.1±1.87.

According to the given results, it can be confirmed, that the screening proved the correctness of the direction we chose – at a dose of 10 mg/kg compounds AO_4, AO_8, AO_9, AO_{11}, AO_{12}, AO_{17}, AO_{23}, AO_{26}, AO_{27}, AO_{30} turned out to be the most active. It has been established, that the substance under the laboratory code AO_{26} (provisional name alkylcarb) showed the maximum analgesic effect of the 30 studied substances. At the same time, the above-mentioned substance in terms of its analgesic effect has a level of activity comparable to the activity of voltaren at a dose of 8 mg/kg and exceeds analgin at a dose of 50 mg/kg

Thus, based on the screening results in the "acetic acid convulsions" test in mice, the leader compound (provisional name alkylcarb) was selected. It became the subject of our further research.

The results of the studies on myotropic spasmolytic activity indicate that the substance alkylcarb exhibits dilator properties (Fig. 5). The studied compound showed minimal dilator activity at a concentration of 10^{-10} mol/l (0.05 ± 0.001 mN) with a maximum at 10^{-2} mol/l (0.11 ± 0.0006 mN).

The concentration reflecting half of the maximum effect was $7.30\times10^{-8} \pm 1.24\times10^{-8}$ 7 mol/l (Table 2).

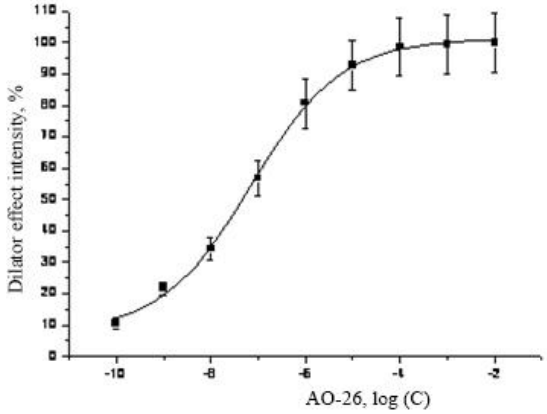

Fig. 5. Dilator activity of alkylcarb on smooth muscle cells of the thoracic aorta pre-contracted with phenylephrine (10^{-6} mol/l)

The experimental studies showed that for drotaverine (Fig. 6), the range of concentrations, used to construct the dose-effect curve, was from 10^{-10} до 10^{-2} mol/l. The spasmolytic effect began to manifest itself at a concentration of 10^{-10} mol/l (0.09 ± 0.0005 mN). The maximum value was recorded at a concentration of 10^{-2} mol/l (0.11 ± 0.0003 mN), while EC_{50} was $1.63\times10^{-8} \pm 0.39\times10^{-8}$ mol/l (Table 2).

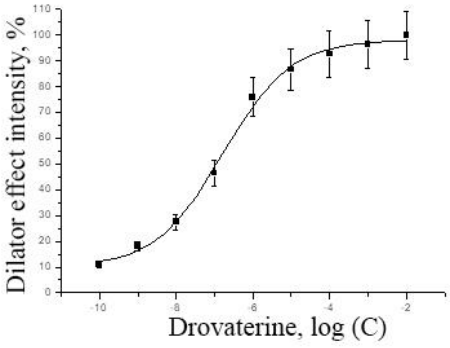

Fig. 6. Dilatatory activity of drotaverine on smooth muscle cells of the thoracic aorta precontracted with phenylephrine (10^{-6} mol/l)

Table 2

The effect of antispasmodics on the dilator activity of muscle cells of the thoracic aorta of rats (M±m), n=6

Drug	E_{max}, %	EC_{50}, mol/l	p
Drovaterine	100	$1.63\times10^{-8} \pm 0.39\times10^{-8}$	<0.05
Alkylcarb	100	$7.30\times10^{-8} \pm 1.24\times10^{-8}$	<0.05

Note: E_{max} – % of maximum effect; EC_{50} – concentration of the drug that causes a reaction corresponding to half of the maximum effect

Thus, the substance alkylcarb has a sufficient antispasmodic effect compared to the classic antispasmodic drotaverine.

4. Discussion

Today, NSAIDs occupy one of the most important positions in clinical practice in Ukraine. The main indications for their prescription are inflammatory processes of various genesis, pain, fever, connective tissue diseases. Every day, more than 30 million people around the world use NSAIDs, and 2/3 of patients use non-prescription NSAIDs. The main requirements for drugs with anti-inflammatory and analgesic effects are effectiveness and safety in use [15]. However, all existing NSAIDs on the pharmaceutical market have restrictions on their use, contraindications and a rather high risk of developing undesirable reactions. The latter occur in 25 % of cases of NSAID use, and induce the development of serious complications in 5 % of patients. Therefore, increasing the safety of patient treatment and preventing the manifestation of undesirable effects, associated with the mechanism of pharmacological action of drugs, can be achieved by synthesizing new original substances with anti-inflammatory and analgesic effects [16]. The work presents the results of screening to establish the analgesic activity of a newly synthesized series of chemical compounds among alkylamides of dihydroquinoline-3-carboxylic acid and the study of the myotropic spasmolytic activity of the leader substance – alkylcarb.

Comparing the effectiveness of the new alkylamide derivative of dihydroquinoline-3-carboxylic acid in different models in mice and rats, it can be stated, that in the "acetic acid convulsion" test, alkylcarb (10 mg/kg, per os) probably reduces the number of convulsions, caused by acetic acid. The level of activity of this compound is compared with the activity of voltaren at a dose of 8 mg/kg and exceeds the activity of analgin at a dose of 50 mg/kg. In in vitro experiments on a model of an isolated fragment of the thoracic aorta of rats against the background of previous constriction with phenylephrine, the substance alkylcarb relieved vasospasm at the level of the comparison drug drotaverine.

Thus, on the basis of the obtained results of own research, the analgesic properties of alkylamides of dihydroquinoline-3-carboxylic acid were studied, which made it possible to recommend for further research the leader substance AO_{26} (alkylcarb) as a promising compound of a new chemical class, which can be considered as a basic compound for creating a potential analgesic.

Limitations of the study. The studies were conducted using the experimental model of "acetic acid convulsions" in mice and in vitro experiments on the model of an isolated fragment of the thoracic aorta of rats under conditions of prior constriction with phenylephrine.

The prospect of further research is the study of the mechanisms of action of alkylcarb.

5. Conclusions

1. The study of the analgesic activity of substances AO_1-AO_{30} in the "acetic acid convulsions" test in mice showed that a compound AO_{26} (provisional name alkylcarb) has the most pronounced analgesic activity when administered intragastrically.

2. In the "acetic acid convulsion" test, alkylcarb (10 mg/kg, per os) reliably reduces the number of convulsions, caused by acetic acid. The degree of activity of this compound is comparable to the activity of voltaren at a dose of 8 mg/kg and exceeds analgin at a dose of 50 mg/kg

3. The effect of a new alkylamide derivative of dihydroquinoline-3-carboxylic acid as a myotropic antispasmodic agent was investigated in in vitro experiments on the model of an isolated fragment of the thoracic aorta of rats under conditions of preliminary constriction with phenylephrine. Alkylcarb substance relieved vasospasm, initiated by phenylephrine, at the level of the comparison drug drotaverine (EC_{50},$7.30\times10^{-8}\pm1.24\times10^{-8}$ mol/l).

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, including financial, personal, authorship, or any other nature that could affect the research and its results, presented in this article.

Funding

The study was performed without financial support.

Data availability

Data will be made available on reasonable request.

Acknowledgement

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