THEORETICAL AND EXPERIMENTAL INVESTIGATION OF ANTIBACTERIAL ACTIVITY OF LIDOCAINE HYDROCHLORIDE AGAINST CLINICAL RESISTANT GRAM-NEGATIVE STRAINS OF BACTERIA

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Introduction

Antimicrobial resistance is one of the greatest hazard in 21st century. The most sensitive to this threat are low and middle-income countries. According to statistic research, antimicrobial resistance infections was a reason to a devastating 4.95 million deaths globally in 2019. This number of deaths from antibiotic resistant bacteria is far exceeds the annual global deaths infections of tuberculosis (1.5 million), malaria (643000), and HIV/AIDS (864000) [1]. The World Health Organization (WHO) has been prognosis that without any intervention in this problem the global deaths of antibiotic resistance could be reach 10 million annually by 2050 [2]. The WHO was marked six main multidrug resistant pathogens that could be a great threat for health care: *Escherichia coli*, *Staphyloccocus aureus*, *Klebsiella pneumonia*, and *Enterobacter faecalis* (ESKAPE) [3].

Lidocaine is a weak alkaline with pKa of 8, it contains amine and aromatic groups that give the ability to have lipophilic properties so in clinical practice lidocaine is applied as a salt of hydrochloric acid. Lidocaine is metabolized to monoethyl glycinelxylidide with P4503A4 in the liver. According to literature source monoethylglycinexylidiole is 80% potent than parent drug whereas other forms of metabolite are absolutely ineffective [4].

In clinical practice, lidocaine is mostly applied as local anesthetic, but also lidocaine possessed anti-inflammatory, antiarrhythmic, anti-nociceptive and antithrombotic action by system administration. The mechanism of action of lidocaine is based a blockade of voltage gated sodium channel that lead to a reversible block of act in potent propagation [5].

According to a literature sources indexed in scientific base of Scopus and Web of Science was found out that lidocaine hydrochloride possessed antimicrobial action against opportunistic pathogenic test strains of *Pseudomonas aeruginosa*, *S. aureus*, *E. coli*, *Proteus vulgaris* [6]. Moreover, it was established that lidocaine hydrochloride inhibited growth of resistant strains of *S. aureus* [7], and *Candida albicans* [8]. However, little attention has been paid to the study of the antibacterial properties against resistant strains of *P. aeruginosa*, *A. baumannii*, *K. pneumonia* and *Enterococcus cloacae*, except that there is no theoretical basis for antibacterial properties of lidocaine hydrochloride against Gram-negative and Gram-positive strains.

So, the aim of the study was to investigate *in vitro* and *in silico* antibacterial activity against clinical multidrug-resistant strains of *S. aureus*, *P. aeruginosa*, *A. baumannii*, *K. pneumonia* and *Enterococcus cloacae*.

Materials and methods

Lidocaine hydrochloride (≥98.0%) and gentamycin sulfate (≥98.0%) was purchased in Sigma Aldrich Company, Lublin, Poland. Chloramphenicol (≥98.0%) was provided by pharmaceutical company "Astrapharm" Kiev, Ukraine; and by pharmaceutical company "Zdravopharm", Kharkiv, Ukraine.

A four clinical isolates of multidrug-resistant Gram-negative bacteria were chosen for research: *P. aeruginosa 18*, *E. cloacea 17*, *A. baumannii 150*, *K. pneumonia 18*. Isolates from clinical samples including tracheal aspirate and broncoalveolar lavage, were provided by Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine, Kharkiv. All strains are stored and accepted by the Head of Museum of strains – O.G. Peretyatko. *P. aeruginosa 18*, *E. cloacea 17*, *A. baumannii 150*, *K. pneumonia 18* were accepted at 01 November 2022.

The minimal inhibition concentration (MIC) is defined as the lowest concentration of an antibacterial agent that completely prevents bacterial growth. The MIC for various extracts was determined using the broth microdilution method [9].

The method of diffusion of the drug into agarcarried out using the method of "wells" [10].

Table 1. Interpretation criteria for microbial sensitivity

Microbial sensitivity	Diameter of the growth retardation zone, mm
High sensitivity	>25
Sensitive	15-25
Low sensitivity	10-15
Not sensitivity	<10

A molecular docking study was conducted using the tool known as AutoDockTools 1.5.6 [11].

The theoretical study of antibacterial activity against Gram-negative strains was used following enzymes: DNA-gyrase (PDB ID: 1KIJ), DHFR (PDB ID: 1RX3), deacytelese (PDB ID: 3UHM), acyl-homoserinelactone synthase (AHS) LasI (PDB ID: 1RO5), acyl-homoserinelactone synthase (AHS) RhI (PDB ID: 1KZF), diguanylate cyclase (PDB ID: 3BRE) structures were obtained from PDB database [12]. The ligand structures of lidocaine hydrochloride (CID_6314); gentamycin (CID_3467); chloramphenicol (CID_5959) were obtained from PubChem database [13]. The active site of the docking protein was identified utilizing the Computed Atlas for Surface Topography of Proteins (CASTp) [14].

To obtain statistical results, the Statistica 10 program was used, the results were analyzed using one-way ANOVA with Tukey's criterion. Differences were considered significant at $p<0.05$.

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Results and Discussion

Theoretical investigation of antibacterial activity of lidocaine hydrochloride against Gram-negative strains was conducted by molecular docking. Bacteria "defense" consists of two lines: a first one represents by following enzymes – DNA-gyrase, DHFR, and deacytelese, the second one represents of enzymes that responsible for formation biofilm – AHS LasI, AHS RhI and diguanylate cyclase. To understand the level of selectivity of inhibition of the active centers of bacterial enzymes by the studied substances, we used the following classification of selectivity [15]: IC50 < 0.001 mM (highly selective); 0.05 > IC50 > 0.01 (medium selectivity); IC50 > 0.05 mM (low selectivity) [15].

Table 2. Molecular docking of the lidocaine hydrochloride and antibacterial drug standards with the DNA-gyrase, DHFR, deacytelese, AHS LasI and RhI, diguanylate cyclase structures of Gram-negative strain

№	DNA-gyrase			
	Ligand	**ΔGbind (kcal/mol)**	**Ki (mmol)**	**Level of selectivity**
1.	Lidocaine hydrochloride	-7.49	0.00324	Medium selective
2.	Chloramphenicol	-6.38	0.02114	Medium selective
3.	Gentamycin	-4.08	1.03	Low selective
№	**DHFR**			
1.	Chloramphenicol	-7.97	0.00143	Medium selective
2.	Lidocaine hydrochloride	-7.49	0.00324	Medium selective
3.	Gentamycin	-6.78	0.01073	Medium selective
№	**Deacytelese**			
1.	Lidocaine hydrochloride	-7.32	0.00433	Medium selective
2.	Gentamycin	-7.45	0.00536	Medium selective
3.	Chloramphenicol	-7.19	0.00346	Medium selective
№	**AHS LasI**			
1.	Chloramphenicol	-10.76	0.00001304	High selective
2.	Lidocaine hydrochloride	-9.03	0.00024	High selective
3.	Gentamycin	—	—	Inactive
№	**AHS RhI**			
1.	Lidocaine hydrochloride	-7.54	0.00296	Medium selective
2.	Chloramphenicol	-5.88	0.04912	Medium selective
3.	Gentamycin	—	—	Inactive
№	**Diguanylate cyclase**			
1.	Chloramphenicol	-6.59	0.01488	Medium selective
2.	Lidocaine hydrochloride	-4.96	0.2305	Low selective
3.	Gentamycin	—	—	Inactive

Notes: ΔGbind – free-binding energy, Ki – concentration inhibited 50% of enzyme activity

Molecular modeling of the identified compounds was performed with the active site of DNA gyrase. The active site was represented by the following amino acids: Arg75, Lys102, Arg135, Asp80. Trp387, Lys109, Asp72 and Thr166. Lidocaine hydrochloride showed medium selectivity to the active site of the enzyme, while antibacterial standards such as chloramphenicol were medium selective inhibitors and gentamicin was a low selective inhibitor. (Table 2)

The next investigated enzyme was DHFR. The active center of this enzyme was represented by the following amino acids: NADP, Tyr110, Asp30, Ile8, Phe34, Ile104, Arg55, Arg60. According to the results presented in Table 2, the free energy of binding decreased in the following order: chloramphenicol (-7.97) < lidocaine hydrochloride (-7.49) < gentamicin (-6.78).

Molecular modeling of the studied compounds was carried out with the active center of Deacytelese. The active center was represented by the following amino acids: Thr190, Lys238, Gly92. Phe191, Leu18, Ala206. Table 2 demonstrates that lidocaine hydrochloride has medium selectivity, whereas antibacterial standards gentamicin and chloramphenicol have medium selectivity, too.

The AHS LasI was next enzyme that was studied by molecular docking. The active center of this enzyme was represented by the following amino acids: Thr142, Thr144, Val143, Phe27, Arg30, Arg104, Met79, Leu102, Phe106, Ser103. According to the results shown in Table 2, the following compounds had the high level of selectivity: chloramphenicol and lidocaine hydrochloride, whereas gentamycine was not interact with active center of AHS LasI.

Molecular modeling of the studied compounds was carried out with the active site of AHS RhI. The active center was represented by the following amino acids: Asp48, Tyr54, Met42. Leu63, Leu56. According to the results of the study and conditional classification, it was established that lidocaine hydrochloride, chloramphenicol had medium selectivity, whereas gentamycin was not interact with protein. (Table 2)

The diguanylate cyclase was the last protein enzyme that was assessed by molecular docking. The

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active center was represented by the following amino acids: Glu254, Glu253, Glu252, Lys327, Arg331, Thr262, Arg198, Arg194. The obtained results showed that there were any high selective inhibitors, in this case chloramphenicol had medium selectivity, whereas lidocaine hydrochloride and gentamycine had the lowest level of selectivity to the active site. (Table 2)

Table 3. Schematic division of antimicrobial drug standards and lidocaine hydrochloride in two categories

№	Compound	DNA-gyrase	DHFR	Deacytelese	AHS LasI	AHS RhI	Diguanylate cyclase	№ of inhibition enzymes of "First line of protection"	№ of inhibition enzymes of "Biofilm"
Antimicrobial drug standards									
1	Chloramphenicol							0	1
2	Gentamycin							0	0
Analyzed compound									
3	Lidocaine hydrochoride							0	1

Further, all antimicrobial drugs and lidocaine hydrochoride were conditionally divided into two categories. The first category included compounds that had a high selectivity for the active site, and the second category included compounds that had medium and low selectivity. This compound separation approach was necessary to clearly identify compounds that interact highly effectively with antimicrobial mechanisms and which compounds work below this level. According to the results shown in Table 3, there was no any compounds that inhibit high selectively all antibacterial mechanisms. The lidocaine hydrochloride and chloramphenicol were high selective inhibitor against biofilm formation mechanism of AHS LasI, whereas gentamicin loses in each mechanism. (Table 3)

Table 4. Antibacterial activity of lidocaine hydrochloride against resistant strains of *P. aeruginosa*, *E. cloacea*, *A. baumannii*, *K. pneumonia*

Sample	Concentration, mmol/L	Diameter of the growth retardation zone			
		P. aeruginosa 18	*E. cloacea 17*	*A. baumannii 150*	*K. pneumonia 18*
Lidocaine hydrochloride	0.12	23.0±0.2	18.0±0.2	24.0±0.1	21.0±0.2
Lidocaine hydrochloride	0.06	15.0±0.1	17.0±0.3	16.0±0.2	16.0±0.2
Lidocaine hydrochloride	0.03	16.0±0.2	18.0±0.2	16.0±0.2	17.0±0.1
Lidocaine hydrochloride	0.003	16.0±0.2	17.0±0.2	16.0±0.2	17.0±0.1
Gentamycin	0.003	growth	17.0±0.2	16.0±0.1	18.0±0.2
Chloramphenicol	0.003	12.0±0.2	19.0±0.1	growth	growth

Lidocaine hydrochloride showed at different concentration high antibacterial activity against resistant Gram-negative strains. At concentration 0.12 mmol/L lidocaine hydrochloride showed high inhibition effect against *P. aeruginosa* (23.0 mm) and *A. baumannii* (24.0 mm), whereas against *E. cloacea* antibacterial effect was lower (18.0 mm). Comparing antibacterial effects of lidocaine hydrochloride of different concentration, it was established that at 0.06, 0.03 and 0.003 mmol/L strain of bacteria *E. cloacea* was most sensitive than other strains. (Table 4)

The gentamycin was only resistant against *P. aeruginosa* strain, comparing antibacterial effect with lidocaine hydrochloride at concentration 0.003 mmol/L it was noticed that gentamycin had stronger inhibition effect against *K. pneumonia* than lidocaine hydrochloride. The chloramphenicol was resistant against *A. baumannii* and *K. pneumonia*, comparing antibacterial effect with lidocaine hydrochloride it was found that *E. cloacea* was more sensitive to the action of chloramphenicol (19.0 mm) than lidocaine hydrochloride. (Table 4)

Table 5. MIC of lidocaine hydrochloride against resistant strains of *P. aeruginosa*, *E. cloacea*, *A. baumannii*, *K. pneumonia*

Sample	MIC, mmol/L			
	P. aeruginosa 18	*E. cloacea 17*	*A. baumannii 150*	*K. pneumonia 18*
Lidocaine hydrochloride	0.00075	0.00075	0.00075	0.00075
Gentamycin	0.006	0.00075	0.00075	0.00075
Chloramphenicol	0.003	0.00075	0.006	0.006

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Lidocaine hydrochloride significantly inhibited resistant strains of *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia* with MIC. Lidocaine had the highest MIC value of 0.00075 mmol/L against *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia.* While gentamycine had lower MIC value than lidocaine hydrochloride against of *P. aeruginosa* (0.006 mmol/L). The chloramphenicol was less active with MIC values of 0.003 mmol/L against *P. aeruginosa* as well as 0.006 mmol/L against *A. baumannii* and *K. pneumonia*.

In our view to inhibit the growth of any bacteria, it is necessary to influence to two lines of "defense". The first line represents by 3 mechanisms: DNA gyrase, DHFR and inhibition of membrane formation; the second line is consisted of mechanisms that form biofilm as AHS LasI and RhI as well as diguanyl cyclase. DNA gyrase is an enzyme responsible for the temporary division of bacterial DNA into two strands, subsequently the replication stage begins. The next important enzyme is DHFR; this enzyme is responsible for the formation of folic acid, which is necessary for the existence of bacteria [16]. One of the main defense mechanisms of any bacteria is its membrane, and gram-negative strains are no exception to the rule. The membrane of gram-negative bacteria contains a special liposaccharide that causes an immune system response and fever. The enzyme UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase is responsible for the synthesis of liposaccharide; this enzyme has no homologs in humans and mammals and is present only in bacteria [17].

The mechanism of biofilm formation in gram-negative bacteria is the formation of a quorum system. The quorum system is a type of cellular signaling that relies on the production and perception of chemical signaling molecules called autodoctors. For the formation of these signal molecules, the protein acyl-homoserine lactone synthetase LasI and RhI is responsible [18]. Also, one of the main stages of biofilm formation is the cell adhesion of bacteria to the surface. Adhesions require a signaling molecule, cyclic di-guanylate monophosphate (c-di-GMP). This molecule coordinates “the transition of the bacterial lifestyle from motile to immobile.” c-di-GMP is synthesized from two molecules of guanylate triphosphate by the enzyme guanylate cyclase [19, 20].

Results has demonstrated that none of antimicrobial drugs highly selectively inhibits all "targets" mechanisms as an investigated compound – lidocaine hydrochloride. In our view, the only one decision to defeat antibiotic resistance is a combination of antimicrobial drug and lidocaine hydrochloride. In experimental study of antibacterial effect of lidocaine hydrochloride, it was noticed that at high concentration of lidocaine hydrochloride there is strong inhibition against of *P. aeruginosa* and *A. baumannii*, whereas at low concentration *E. cloacea* and *K. pneumonia* were more sensitive. In our view, it could be relating with own sensitivity of bacteria as each strain of bacteria has own physiology, metabolism and structure. In the case of MIC investigation lidocaine hydrochloride showed better results than antimicrobial standards such as gentamycin and chloramphenicol against all resistant strains of *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia*.

Conclusions. It has conducted theoretical and experimental studies of antibacterial effect of lidocaine hydrochloride. The theoretical results demonstrated that lidocaine hydrochloride highly selectively inhibited only one enzyme – AHS LasI. According to experimental results, it was shown that lidocaine hydrochloride effectively inhibited resistant strains of *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia*. So, lidocaine hydrochloride is a perspective substance for elimination resistance of antibiotics.

Conflict of interest: authors have no conflict of interest to declare.

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Theoretical and experimental investigation of antibacterial activity of lidocaine hydrochloride against clinical resistant gram-negative strains of bacteria

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Introduction. Today, antimicrobial resistance is the number one problem worldwide. One of the first mentions of the emergence of antibiotic-resistant strains of bacteria in humans was obtained during military conflicts in Iraq and Afghanistan 20 years ago. In addition, according to the latest data, it has found that *Acinetobacter baumani, Pseudomonas aeruginosa*, *Klebsiela pneumonia* and *Enterococcus cloacae* are predominant among all isolated resistant pathogens. So, the search of new antibacterial drug that can deal with antimicrobial resistance is a task number one. **The purpose of the study** was to investigate *in vitro* and *in silico* antibacterial activity against clinical multidrug-resistant strains of *Staphylococcus aureus*, *P. aeruginosa*, *A. baumannii*, *K. pneumonia* and *E. cloacae*. **Materials and methods.** The object of the study was lidocaine hydrochloride. The molecular docking was performed using AutoDockTools 1.5.6; antibacterial effects were evaluated by the well and "dilution" methods method. Isolates were obtained from clinical samples including tracheal aspirate and broncoalveolar lavage. **Results**. Lidocaine hydrochloride was shown high selectivity to AHS LasI, Experimental research was demonstrated that against

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resistant strain of *P. aeruginosa* lidocaine hydrochloride inhibited growth – from 23.0±0.2 to 16.0±0.2 mm, against *A. baumannii* – from 24.0±0.1 to 16.0±0.1 mm, against *E. cloacea* – from 18.0±0.2 to 16.0±0.2 mm, *K. pneumonia* – from 21.0±0.2 to 16.0±0.2 mm, respectively. The minimum inhibitory concentration (MIC) values of lidocaine hydrochloride for *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia* was 0.00075 mmol/L. **Conclusion.** It has conducted theoretical and experimental studies of antibacterial effect of lidocaine hydrochloride. The theoretical results demonstrated that lidocaine hydrochloride highly selectively inhibited only one enzyme – AHS LasI. According to experimental results, it was shown that lidocaine hydrochloride effectively inhibited resistant strains of *P. aeruginosa, E. cloacea, A. baumannii, K. pneumonia*. So, lidocaine hydrochloride is a perspective substance for elimination resistance of antibiotics.
Key words: lidocaine hydrochloride, multi-drug resistant, Gram-negative strains, molecular docking

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