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Research Article

Comparative Activity of Carbapenems (Biapenem/Merapenem) in the Therapy of Carbapenemase-Producing Enterobacterales

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Abstract

Carbapenem antibiotics continue to hold a leading position in the treatment of hospital-acquired infections. However, since the mid-2000s, the importance of this group of antibiotics has gradually declined due to the spread of resistance to them. Although resistance to carbapenems is mediated by various factors, the most important is the production of β–lactamases, in particular carbapenemases. All beta-lactamases are divided into four classes. In the Russian highest percentages are for OXA-48 and NDM, at 75% and 18%, respectively. In 6% of cases, both carbapenemases OXA-48+NDM were detected, and the frequency of KPC carbapenemase was 1%. Data on the sensitivity of bacteria producing carbapenemases to biapenem and meropenem is contradictory. In this regard, the purpose of this study was to compare the activity of bipenem and meropenem against Enterobacterales (Klebsiella pneumonia and Escherichia coli) that produce carbapenemases. The study included 32 isolates of gram-negative flora of the enterobacterales family. Sensitivity testing for biapenem and meropenem was performed using the method of microdilution in a liquid culture medium in accordance with GOST R ISO 20776-1-2022, with determination of the minimum inhibitory concentration (MIC). The identified carbapenemases in enterobacterales were distributed as follows: NDM carbapenemase producers-15 isolates, OXA-48 carbapenemase producers-13 isolates, NDM+OXA-48 carbapenemase producers-1 isolates and KPC carbapenemase producers-3 isolate. Four of the fifteen NDM-producing isolates, the MIC for biapenem was in the intermediate zone, i.e. less than 8 mg/L, while the MIC for meropenem was in the non-sensitive zone for all fifteen isolates, i.e. more than 8 mg/L. Among the OXA-48-producing isolates, three of the thirteen showed susceptibility to biapenem, with an MIC of less than 2 mg/L, while only one isolate showed susceptibility to meropenem, with an MIC in the intermediate zone (4-8 mg/L). For the NDM+OXA-48 and KPC -producing isolates the MIC of both antibiotics were in the non-susceptible zone, i.e. > 8 mg/L. Biapenem is a new member of the carbapenem antibiotics, showing good activity against Enterobacteriaceae producing carbapenemases NDM and OXA-48 types. Given the greater sensitivity to it among the isolates of this type of bacteria, this drug may have an advantage among other members of the carbapenems.

Keywords

Biapenem, Meropenem, Enterobacterales, Carbapenemase

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1. Introduction

Carbapenem antibiotics continue to hold a leading position in the treatment of hospital-acquired infections. Due to their extremely broad spectrum of action and ability to overcome bacterial resistance mechanisms, carbapenems have long been the most reliable treatment for severe hospital-acquired infections. However, since the mid-2000s, the importance of this group of antibiotics has gradually declined due to the spread of resistance to them [1, 2]. In the Russian Federation, over a 5-year period from 2012 to 2016, according to the available data, the proportion of enterobacteria that are insensitive (resistant and moderately resistant) to meropenem increased from 1.28% to 13.84%, to imipenem from 7.69% to 14.11%, and to ertapenem from 8.97% to 25.84% [3].

All the diversity of mechanisms of formation of antimicrobial resistance can be combined into several principal directions:

1. Target modification. In the case of β-lactam antibiotic, the specific mechanism of resistance is the change in the structure of the targets of the action of antibiotics – penicillin-binding proteins (PBP). This in turn leads to a decrease in the affinity (relevance) between PBP and the antibiotic molecule and, as a result, to an increase in the values of the minimum inhibitory concentrations (MIC) of antibiotics. It is also possible for bacteria to acquire new low-affinity PBPs. β-Lactam resistance associated with PBP modification is most common among gram-positive bacteria (Streptococcus spp. and Staphylococcus spp.) [4], while among gram-negative bacteria, this mechanism is found in Neisseria gonorrhoeae and Haemophilus spp.

2. Decreased permeability of external structures. In the case of gram-negative bacteria, in order to reach its target, a β-lactam antibiotic molecule must cross the outer membrane, a structure that is almost impermeable to water-soluble compounds. Normally, β-lactams enter gram-negative bacteria through porin channels formed by porin proteins or outer membrane porins (OMPs). Modification, reduced expression, or complete loss of OMPs leads to an increase in MICs. Loss of OMP is observed in Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii [5]. But even complete loss of porins does not always lead to the formation of a resistant phenotype, in most cases this is achieved in combination with an increase in the expression of β-lactamases [6].

3. Active excretion (efflux). The mechanism of resistance is the excretion of various substances from the periplasmic space of bacteria into the external environment. If the rate of excretion is higher than the rate of drug penetration into the cell, a resistant phenotype is formed [7]. Efflux pumps are an important mechanism of resistance in many gram-negative pathogens, particularly Acinetobacter spp. and P. aeruginosa. In P. aeruginosa, the MexA-MexB-OprD system, combined with reduced membrane permeability, can lead to resistance to many antibiotics (penicillins, cephalosporins, quinolones, tetracyclines, and chloramphenicol) [8].4. Inactivation. Enzymatic hydrolysis is one of the main mechanisms of bacterial resistance to β-lactam antibiotics. To date, more than 1,000 β-lactamases have been described, differing in substrate specificity, sensitivity to inhibitors, and gene localization. The emergence and spread of new β-lactamases among clinically significant bacteria has significantly influenced the development of this group of antibiotics [9].

Although resistance to carbapenems is mediated by various factors, such as the loss of outer membrane porins, active elimination of an antibacterial drug (efflux), and synthesis of carbapenemases from a bacterial cell (efflux), the most common is the production of β–lactamases, in particular carbapenemases [10].

Depending on the structure of the active site, beta-lactamases (including carbapenemases) are divided into two groups: serine beta-lactamases and metal beta-lactamases. The first have a serine amino acid in their active site, while the second have a zinc atom.

In addition, depending on the amino acid sequence, beta-lactamases are divided into four classes [11]. Classes A, C, and D are serine beta-lactamases, while class B is a metal beta-lactamase (Figure 1).

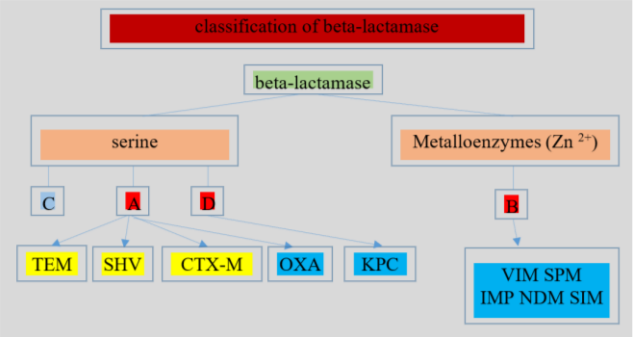

Figure 1. *Classification of the beta-lactamase family.*

Of the various carbapenemases, three groups are of the greatest importance and prevalence. Two of them are serine beta-lactamases: KPC-type (more than 100 variants) and OXA-48-type (about 60 variants), and one is a metal-beta-lactamase NDM-type (more than 40 variants). Less important are carbapenemases of the IMI, VIM, SME, IMI, NMC and other groups [12]. The group affiliation of carbapenemases detected among nosocomial isolates in the Russian Federation is presented in Figure 2. As can be seen from the data, the highest percentages are for OXA-48 and NDM, at 75% and 18%, respectively. In 6% of cases, both carbapenemases OXA-48+NDM were detected, and the frequency of KPC carbapenemase was 1% [13].

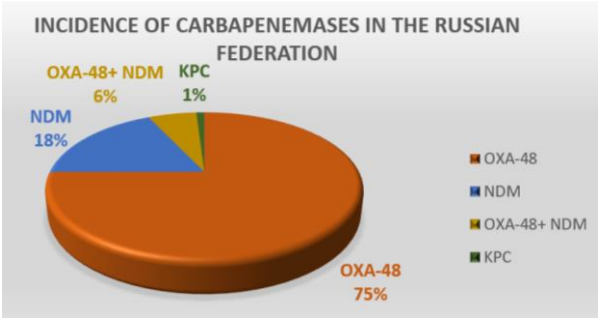

Figure 2. *Incidence of carbapenemases in the Russian Federation.*

In our study, the frequency of isolated NDM carbapenemase was significantly higher, but it generally reflects the group prevalence of carbapenemases in the Russian Federation.

According to the literature, the activity of carbapenems differs depending on the producers of carbapenemases by bacteria. In his work, Livermore D.M. points out that bipenem has a significantly lower minimally inhibitory concentration (MIC) in relation to NDM, KPC and OXA-48 producers carbapenemases, compared to other carbapenems, such as meropenem [14]. This fact is also confirmed by Gordina E.M. in her work [15]. At the same time, according to R.S. Kozlov, biapenem does not have any advantages over carbapenems such as meropenem/imipenem, and is comparable to them in terms of activity [16].

2. The Purpose of the Study

In this regard, the purpose of this study was to compare the activity of bipenem and meropenem against Enterobacterales (Klebsiella pneumonia and Escherichia coli) that produce carbapenemases.

3. Material and Methods of the Study

3.1. Sampling of Isolates

The study included 32 isolates of gram-negative flora of the enterobacterales family (Klebsiella pneumonia - 18 isolates, Escherichia coli - 14 isolates) isolated from the sputum of the tracheobronchial tree in patients with clinical and laboratory data of the inflammatory process. Sensitivity testing for biapenem and meropenem was performed using the method of microdilution in a liquid culture medium in accordance with GOST R ISO 20776-1-2022 [17], with determination of the minimum inhibitory concentration (MIC).

3.2. Detection of Carbapenemases

The genes of carbapenemases of the KPC, OXA-48, and MBL groups (in particular, NDM) were determined using the AmpliSens MDR KPC/OXA-48-FL and AmpliSens® MDR MBL-FL reagent kits by PCR with hybridization-fluorescence detection in real time. The analysis uses DNA samples obtained by extraction from bacterial cultures, positive hemocultures, and mixtures of cultures after the initial sowing of clinical material (liquor, sputum from the tracheobronchial tree, wound discharge, etc.) on solid or liquid media, as well as from urine and swabs from the mucous membranes of the oropharynx and rectum.

3.2.1. Principle of the Method

The method detects DNA fragments of carbapenemase genes of KPC, OXA-48 and NDM groups by PCR with hybridization-fluorescent detection. It consists of two stages: DNA extraction from biological samples is carried out in the presence of an internal control sample. This allows to control the procedure for each sample. Next, with the obtained DNA samples, amplification is performed using specific primers and the enzyme Taq polymerase. The reaction mixture contains fluorescently labeled oligonucleotide probes. They hybridize with the complementary region of the target DNA. As a result of this process, the fluorescence intensity increases. This allows the accumulation of a specific amplification product to be detected by measuring the intensity of the fluorescence signal. The results of amplification of carbapenemase gene fragments of the studied groups are recorded in different channels of fluorescence detection (FAM-KPC, JOE-OXA-48, Cy5-NDM). The channel for the fluorophore ROX determines the product of amplification of the VKO DNA (internal control sample).

3.2.2. Analysis and Interpretation of Results

The results are analyzed using special software that is used for PCR with real-time detection. The graphs of the accumulation of the fluorescent signal in four channels are considered:

The FAM channel records a signal indicating the accumulation of the product of amplification of fragments of genes of carbapenemases of the KPC group. - The JOE channel records a signal indicating the accumulation of the product of amplification of fragments of genes of carbapenemases of the OXA-48-like group. - The Cy5 channel displays a signal for the fluorophore indicating the accumulation of the product of amplification of fragments of genes of NDM group of MDB. - The ROX channel tracks a signal indicating the accumulation of the product of amplification of internal control DNA. The results are interpreted by the presence or absence of the fluorescence graph crossing the threshold line set at the level of exponential rise of the signal. This determines the presence or absence of the threshold cycle Ct value for a given DNA target in accordance with the result table column attached in the insert of the reagent kit.

4. Research Results

The identified carbapenemases in enterobacterales were

distributed as follows: NDM carbapenemase producers-15 isolates, OXA-48 carbapenemase producers-13 isolates, NDM+OXA-48 carbapenemase producers-1 isolates and KPC carbapenemase producers-3 isolate. The distribution of the susceptibility of carbapenemase-producing isolates to MICs of bipenem and meropenem is shown in Figures 2, 3. It should be noted that the European organization EUCAST does not provide criteria for sensitivity to biapenem. Based on pharmacodynamic studies, the following criteria for sensitivity to this drug have been established: resistant strains with MIC > 8 mg/L, sensitive strains with MIC ≤ 2 mg/L, and intermediate strains with MIC of 4-8 mg/L, which are considered to be sensitive at higher doses [18].

The study revealed the following. Four of the fifteen NDM-producing isolates, the MIC for biapenem was in the intermediate zone, i.e. less than 8 mg/L, while the MIC for meropenem was in the non-sensitive zone for all fifteen isolates, i.e. more than 8 mg/L (Figure 3).

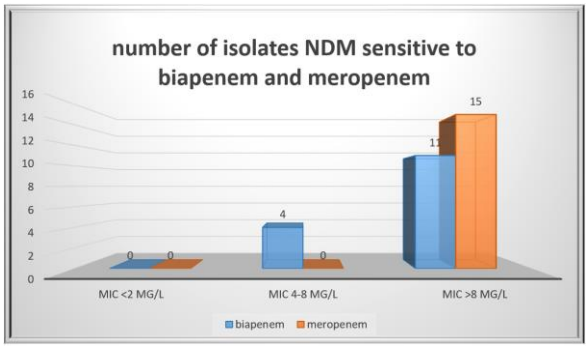

Figure 3. *On the abscissa- MIC carbapenems; on the ordinate- number of isolates.*

Among the OXA-48-producing isolates, three of the thirteen showed susceptibility to biapenem, with an MIC of less than 2 mg/L, while only one isolate showed susceptibility to meropenem, with an MIC in the intermediate zone (4-8 mg/L) (Figure 4). For the NDM+OXA-48 and KPC -producing isolates the MIC of both antibiotics were in the non-susceptible zone, i.e. > 8 mg/L.

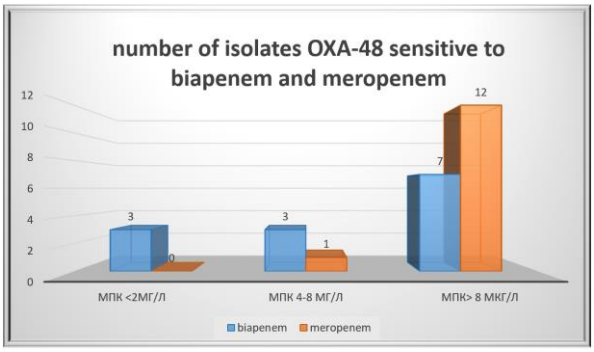

Figure 4. *On the abscissa- MIC carbapenems; on the ordinate- number of isolates.*

5. Conclusions

Biapenem is a new member of the carbapenem antibiotics, showing good activity against Enterobacteriaceae producing carbapenemases NDM and OXA-48 types. Given the greater sensitivity to it among the isolates of this type of bacteria, this drug may have an advantage among other members of the carbapenems. The results of the study we conducted are comparable with some previously performed works, showing greater sensitivity of isolates producing carbapenemases A and B classes to biapenem and the lack of sensitivity of carbapenemase D-producing isolates to this antibiotic [18]. The reason for the observed differences is currently unknown, but it is possible that bipenem is more resistant to carbapenemase hydrolysis compared to other carbapenems. [19].

Abbreviations

PBP	Penicillin-Binding Protein
OMP	Outer Membrane Porin
MIC	Minimum Inhibitory Concentration
PCR	Polymerase Chain Reaction
DNA	DeoxyriboNucleic Acid

Author Contributions

Doev Denis Petrovich: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing

Conflicts of Interest

The author declares that there is no conflict of interest.

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