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Linezolid use in Medicine Therapy against Multiresistant Bacteria-A Review

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Abstract

After the description of an element with ability to combat the infectious processes originating from bacteria, starts a race for survival between the interrelationship of species, bacterial and human. With the evolution scientific-technical, the man was able to synthesize new antibacterial substances, on the other hand the mechanisms of gene evolution enabled the emergence of multidrug-resistant bacteria. Some of this organisms are frequent on hospital environment and have high adaptability to new drugs, such as *Staphylococcus aureus* and *Enterococcus* spp. resistant to oxacillin and vancomycin, considered drugs of choice against multidrug-resistant microorganisms. So, a new antibiotics class was developed, superior to vancomycin and oxazolidinone, the linezolid. Thus, the present study aimed at understanding the use of linezolid in drug therapy against multi-resistant bacteria. To perform this study, a literature review of last 10 years was performed. In 2002, after the liberation of the use of linezolid as treatment for infectious processes against gram-positive bacteria, this drug was commonly used throughout the world. Similarly, the pressure of natural selection stood out, and there were records of resistant strains to linezolid. As prospects for control of infections caused by these resistant strains, was approved by the FDA in 2014 the use of drugs with linezolid resistant anti-strains activity. However, we conclude that, in addition to natural selection and genetic variation process, human behavior regarding the use of antibiotics, increases the selection of resistant microorganisms to antibiotic, including linezolid.

Keywords: Multiresistant bacteria; Linezolid; Antibiotic; New drugs; Medicine therapy

Introduction

Antimicrobial agents are natural or synthetic compounds capable to inhibit the growth (bacteriostatic), or cause the death of microorganisms (bactericidal) [1-3]. In the last years, there was an increase of resistant microorganisms to various types of drugs used as treatment, called multidrug resistant bacteria [4], that had a strong impact on public health, due the increase of patients infected cases since 2000 [4].

For gram-positive bacteria, especially *Staphylococcus aureus*, oxalizidonone has been developed as a promising drug in the fight against infections caused by multi-resistant gram-positive bacteria [5,6]. These drugs present a new mechanism of action on bacterial protein synthesis, acting in inhibition of N-formylmethionyl-tRNA binding to the 70S ribosomal subunit [7].

Linezolid is a synthetic antimicrobial, belonging to the class of oxazolidinones that acts in the protein synthesis, specifically in the binding to the 50S subunit of the ribosome, with bacteriostatic action [7-9]. Due to this mechanism of action, it has a significant activity against multi-resistant Gram-positive bacteria, and great importance on treatment of MRSA (Methylcycline-Resistant *Staphylococcus aureus*) and VRE (Vancomicyne Resistant *Enterococcus*). However, it has no action against resistant Gram-negatives bacteria [10-13].

Although linezolid presents a huge potential for treatment against multi-resistant gram positive *cocci*, some *Staphylococcus aureus* strains were isolated presenting resistance to linezolid, however it is a rare clinical phenomenon. Most of reported cases have been associated with deep organ infections, presence of foreign body, nosocomial outbreaks and/or prolonged therapy with linezolid (for more than three weeks) [14]. The mechanism of resistance to linezolid most described is the specific nucleotides substitution in rRNA 73, being the number of genes mutated is related to the level of resistance to the drug. In response to linezolid resistance, a new oxazolidinone have being developed ((5R)-3-{3-fluoro-4-[6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl] phenyl}-5-(hydroxymethyl)-1,3-oxazolidin-2-one), it acts on the inhibition of protein synthesis and has a broad spectrum [15,16]. But these new drugs have little clinical use, preventing the development of new and powerful mechanisms of resistance.

Therefore, due to the huge importance of linezolid as an alternative drug in treatment of multiresistant bacteria, it is essential to broad our knowledge about the main aspects of linezolid use as a therapeutic drug, being the main goal of this work. To do this, first of all it was necessary to approach the general mechanisms of bacterial resistance to understand the context which linezolid was developed as a therapeutic strategy; After, was made a brief description of the target microorganisms of this drug, as well as its general mechanisms of action and resistance, and finally the therapeutic strategy in cases of linezolid resistance.

To develop this work, a bibliographic survey was done in databases periodicals, such as medical bibliography (MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS) and PUBMED since 2002. Work was done in this period because it is a current theme and has been attracting researcher's attention. The inclusion criteria were: original articles with identification of topics that address characteristics of multiresistant bacteria, as well as definitions and applications of the drug Linezolid.

Development

General mechanisms of bacterial resistance

To broad our knowledge about the linezolid mechanism of action, first of all it is necessary to understand the context of this medicine was developed. Therefore, it is of fundamental importance the understanding of the resistance mechanisms developed by the bacteria, where it appears bacteria multiresistant to the usual antibiotics.

Microbial resistance is a natural biological event (natural selection) that is a result of the inappropriate use of antibiotics [17]. Bacterial resistance can occur through several mechanisms of action such as: The mutation and transference of DNA; Impermeability to drugs; Inactivation or alteration of the antibiotic binding site; Efflux pumps and biofilms [18]. In paragraphs bellow, will be described some of the main mechanisms of drug resistance in bacteria [19].

The emergence of resistance occurs on mutation cause replication of bacteria. During this process, errors may occur that modify the DNA coding sequence and consequently cause modification on the information contained in original DNA sequence, producing cells with a specific mutation that will be transferred to future generations. Some mutations are beneficial to the bacteria such as resisting the action of an antibiotic, offering a competitive advantage in their environment, but are the less frequent forms of extrinsic resistance [20,21]. As chromosome resistance depends on spontaneous mutation, a rare event, it is almost always directed to a single drug and the genes are transferred with relatively low frequency. Therefore, its clinical impact is lower than that of the plasmidial resistance [21].

The most important bacterial genetic mechanism of antibiotics resistance is the transfer of mobile genetic elements between bacterias this cellular event can occur in 4 distinct ways: Conjugation; Transduction; Transformation and Transposition [19,21].

In conjugation, the resistance genes transfer occurs through plasmids (which are small circular DNA molecules), with necessarily contact between the bacterial cells. Certain plasmids have genes responsible for the synthesis of enzymes that destroy an antibiotic before it destroys the bacteria. These are called R plasmids (antibiotic resistance), which have genes that can be transferred from one bacteria to another (factor F) [20,21]. When two or more types of plasmids R are present in the same bacteria, the genes of one can pass to the other organism by gene recombination through the processes of conjugation, transformation or transduction. These mechanisms cause the emergence of R plasmids presenting several resistance genes to different antibiotics [21].

In transduction occurs the transfer of resistance genes through a virus (bacteriophage), on this process the phage coat protects DNA from environment action, so this cellular process is not affected by nucleases in the environment [22]. The phage ability to mediate the transduction is related to the life cycle, so the accidental bacterial DNA incorporation by the bacteriophage occurs during the cellular infection process. At the end, after cell lysis, the bacteriophage acts as a vector and, upon infecting a new cell, can introduce DNA containing the resistance gene making it resistant to the drug [22,23].

In the transformation occurs the transference of resistance genes from the donor to the receptor cell, without contact between the cells. In this biological process, a recombinant or not vector is inserted into a bacteria, which contains the resistance genes. The bacteria are transformed by mechanical action (electroporation) or membrane pore formation (calcium chloride) [22]. To occur this process is necessary that the donor cell is in a competence stage, able to receive this material. It is a process of little clinical importance, since it only occurs in extremely favorable conditions [23].

Transposition of resistance determining genes can occur by transference one plasmid to another, to the chromosome or to a bacteriophage, being the transposon the element responsible for the transfer [21,24]. The transposons were discovered in 1974, on this occasion was observed most of the resistance genes considered plasmid or chromosomic are located on transposons and have the properties of rapid dissemination within or between cell [20,21]. Transposons are highly mobile DNA segments and encoding the enzyme transposase - Responsible for its transfer to other segments of DNA. They are promiscuous, create variations and invade various sites of the host DNA, but sometimes exaggerate, producing lethal mutations [21,24].

Other natural mechanism of bacterial resistance to antibiotics are drug impermeability, this mechanism is developed by several Gram negative bacteria that are resistant to penicillin presenting modifications in penicillin binding proteins or absent drug impermeability. In the case of sulfonamides the microorganism may also have a lower drug permeability [19].

Inactivation is an important mechanism, which drugs are inactivated by specific enzymes, produced by the resistant organisms. For example, penicillinase (β-lactamases) is an enzyme that cleaves the β-lactamic ring inactivating the drug. Other drugs may be inactivated as a result of modifications introduced by the microorganism, such as the addition of chemical clusters. Thus, many bacterias are capable of promoting the antibiotics phosphorylation or acetylation [21,25,26].

The antibiotic binding site (target) modification occurs when antibiotics bind to bacteria specific sites, if this site is changed, the antibiotic does not affect the binding and becomes inefficient against the microorganism. This physico-chemical alteration decreases the affinity of the drug for the site and causes loss of antimicrobial activity. As an example of this, mechanism of action is seen in the literature methicillin resistant *Staphylococcus aureus*, and penicillin resistant *Streptococcus pneumoniae* [27,28].

Another important mechanism is the pumping to the external medium through the efflux of the drug. In this cellular process, occurs

the expulsion of the antibiotics by cell, contributing to an inadequate concentration of the drug and consequently, ineffective action. As an example, can be mentioned the resistance to tetracycline's in enteric bacteria [25,29].

Another aspect that has been increasingly taken into account is biofilms occurrence and their importance in antimicrobial therapy. Of course, use of antibiotics, be more effective, it is necessary a better understanding of biofilms naturally formed in our body, because only from the elucidation of the ecology of the natural biofilms, we will have a better chance to treat adequately the various infectious diseases [17].

Gram positive multiresistant bacteria

Approximately 10% of infections on hospitalized patients are commonly caused by Gram positive multiresistant bacteria, such as MRSA (*Staphylococcus* resistant to methylicine) and VRE (*Enterococcus* vancomicyne resistant). The identification of the organism have special significance because it can cause large outbreaks in hospitals [30]. Below we will briefly discuss about the major groups of gram positive bacteria, which are multiresistant to various antibiotics and often is used Linezolid as alternative therapy, being first approached about the genre *Enterococcus*, after about the species *Staphylococcus aureus* [30,31].

The genre *Enterococcus* is represented by nine species, being two of these the main cause of most infections: *Enterococcus faecalis* (more frequent in Brazil), *Enterococcus faecium*. It is saprophytic in nature and inhabit the soil, food, gastrointestinal tract, genitourinary tract, grow in salt solutions and in detergents, can be aerobic or anaerobic facultative cocci gram-positive [30]. *Enterococcus* can survive up to 7 days in different types of environment, it is naturally resistant to several antimicrobials and, in several clinical situations, patients with infection require two antimicrobials for treatment [32,33].

The prevalence of *Enterococcus* sp. Vancomycin-resistant (VRE) is emerging in hospitals around the world, and the units that most frequently present patients infected/colonized by VRE are transplantation units, oncological units and mainly in ICUs (Intensive Care Units) [30,34,35]. In Brazil, some prospective studies in ICUs show rates between 14 and 25% of rectal colonization, usually in patients with prior antibiotic use (vancomycin) and with a history of long hospital stay. Moreover, outbreaks of hospital infections have occurred in several Brazilian hospitals - mainly caused by *Enterococcus faecalis*, which are often also sensitive to ampicillin [30,36].

Staphylococcus aureus is an agent of bloodstream infections, related to catheters, skin and soft tissue infections, however; also is one of the most frequent agents of pneumonias associated with mechanical ventilation. Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause large and costly epidemic infections of difficult treatment and control, as it is an organism multiple intrinsic resistance to methicillin, oxacillin, cephalosporins, imipenem and aminoglycosides [32,33,37].

The increase in MRSA hospital infections was accompanied by resistance to a greater number of antibiotics, such as aminoglycosides, quinolones, macrolides and tetracyclines. The concern is focused on the emergence of microorganisms with intermediate resistance to vancomycin, as this is one of the treatments of choice for MRSA [38,39].

Linezolid on treatment of multiresistant bacteria

Linezolid is a synthetic antimicrobial, belonging to oxazolidinones, a new family of antimicrobials, which shows superiority to vancomycin. It acts on the protein synthesis, binding to the 50S subunit of the ribosome, interrupting the translocation process and has bacteriostatic action [7-9]. Due to the fact that presents significant activity against multiresistant Gram-positive bacteria, it has great importance in the treatment of MRSA and VRE, but has no action against resistant Gram-negatives [7-9,40].

It can be administered intravenously or orally, thus having a bioavailability of 100%, the recommended dose is 600 mg every 12 hrs. It is metabolized in the liver, however, it does not present interactions with cytochrome P450, reaching high concentrations in the lungs, bones, muscles, cerebrospinal fluid and skin. The adverse effects are headache, diarrhea, insomnia, constipation and vertigo, as well as haematological effects such as thrombocytopenia, especially in prolonged treatments, being reversible with the suspension of the drug [7-9,41-43]

Low levels of resistance were observed and may be associated with mutations in ribosomal RNA, however, it is suggested to perform susceptibility tests to this antimicrobial before the start of antibiotic therapy [7,9,44,45].

Isolates of *Staphylococcus aureus* exhibiting resistance to linezolid have been selected *in vitro*, however it is still a rare clinical phenomenon. Many of the reported cases of infections caused by linezolid-resistant MRSA have been associated with deep organ, foreign body, nosocomial outbreaks, and/or prolonged therapy with Linezolid (usually more than three weeks) [14,46].

The most common linezolid resistance mechanism among MRSA isolates is the presence of specific nucleotide substitution in ribosomal RNA 73, the number of mutated genes depends on the dose and duration of exposure to linezolid and is related to the level of resistance to linezolid. Mutations associated with ribosomal proteins also affect the activity of linezolid. It has recently been discovered that an RNA methyltransferase, called Cfr, is the cause of a new phenotype of resistance to phenicols and clindamycin, which also confers resistance to oxazolidinones) [14,46].

Recently, a new oxazolidinone (tedizolid) was demonstrated ((5R)-3-{3-fluoro-4-[6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl] phenyl}-5-(hydroxymethyl)-1,3-oxazolidin-2-one), that acts through the inhibition of protein synthesis and has broad spectrum, including strains resistant to linezolid. In July 2012, tedizolid had completed a phase III clinical trial. Subsequently, a second clinical trial, both trials compared a six-day drug therapy of tedizolid to a concentration of 200 mg once daily, compared to the drug activity of linezolid at a concentration of 600 mg twice daily, the results demonstrated the efficacy of tedizolide. Thus, Tedizolid was approved by the FDA on June 20, 2014 for the treatment of methicillin-resistant *Staphylococcus aureus* skin infections. It can be taken orally and given *via* injection IV [16,47].

Conclusion

Although there is a general characterization of multiresistant microorganisms, specific characteristics are incorporated into each, which may result in different classes of organisms controlled by specific classes of antibiotics, such as linezolid, for gram-positive and multiresistant bacteria.

Linezolid works in protein synthesis, binding to the 50S subunit of the ribosome, interrupting the translocation process and has a bacteriostatic action. It has good drug tolerance, low adverse effects and broad spectrum of action, and is mainly used against multiresistant gram-positive bacteria, however the use of linezolid in drug therapies allowed the selection of drug resistant strains.

Therefore, we can conclude in a general way that the mechanisms of the process of natural selection and genetic variations, as well as the human behavior regarding the use of antibiotic therapy, led to the natural selection of multiresistant strains associated with nosocomial infections, including linezolid. Currently, there are investments for the development of new drugs capable of combating strains resistant to linezolid, and other new generation antibiotics. But as long as there is no conscious in use of these drugs, the question of the natural selection of multiresistant bacteria will not be solved.

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