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An introduction of Antibiotic Resistance and Bacterial Resistance of Aminoglycoside Antibiotics

[1]Abhijit Ashok Bansod; [2]Pooja Wankhede; [3]Dr. Gajanan S. Sanap; [4]Ravindra G. Rathod.

[1,2,3,4] LBYP College of Pharmacy, Chh. Sambhajinagar- 431111, Maharashtra, India

A B S T R A C T

Resistant bacteria spread by Natural selection when antibiotics fail to Halt their reproduction while removing their Drug-sensitive competitors with Gram-negative pathogens the antibiotic crisis is currently more serious than with the Gram-positives. the World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century. Resistance to aminoglycosides may occur based on several mechanisms enzymatic modification and inactivation of the aminoglycosides, mediated by aminoglycoside acetyltransferases, nucleotidyl transferases, or phosphotransferases and commonly observed across gram-positive and -negative bacteria. Aminoglycoside has wide spectran activity against gram positive as well as gram negative bacteria. Gentamicin, Amikacin, Tobramycin, Neomycin, and Streptomycin. these are drugs used for antibacterial treatment.

This review article focus on safety and efficacy of aminoglycoside in use as antibiotic. As we know antibiotics are widely used in now a days for the treatment of various bacterial infection, hence, development of resistence in one of the most important factor to be consider.

Keywords: Antibiotic Resistance, Bacterial Resistance , aminoglycoside ,Antibiotics, gram positive.

Introduction

This large and important family of compounds virtually unusable. Resistance is primarily mediated by three classes of enzymes, typically residing on transposable elements in resistant bacteria. These enzymes, the phosphotransferases, acetyltransferases and adenyl transferases, chemically modify the aminoglycosides, which either interferes with drug transport or the binding of the drug at the site of antibacterial action, the 30S ribosomal subunit. Antimicrobial resistance in bacterial pathogens is a worldwide challenge associated with high morbidity and mortality.

Multidrug resistant patterns in Gram-positive and -negative bacteria have resulted in difficult-to-treat or even untreatable infections with conventional antimicrobials. Because the early identification of causative microorganisms and their antimicrobial susceptibility patterns in patients with bacteremia and other serious infections is lacking in many healthcare settings, broad spectrum antibiotics are liberally and mostly unnecessarily used**(1)** The discovery, commercialization, and routine administration of antimicrobial compounds to treat infections revolutionized modern medicine and changed the therapeutic paradigm. Indeed, antibiotics have become one of the most important medical interventions needed for the development of complex medical approaches such as cutting-edge surgical procedures, solid organ transplantation, and management of patients with cancer, among others. Unfortunately, the marked increase in antimicrobial resistance among common bacterial pathogens is now threatening this therapeutic accomplishment, jeopardizing the successful outcomes of critically ill patients.

In fact, the World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century **(2)**. Antibiotics are available that effectively inhibit bacterial cell wall synthesis, protein synthesis, and DNA replication.. This horizontal gene transfer(HGT) can occur between very different Bacteria. Antibiotic use drives the evolution of re-Sistance [4]

MDR Gram-negatives are increasingly prevalent also in the community, including Escherichia coli producing extended-spectrum beta-lactamases (ESBLs) [7,8], and Neisseria gonorrhoeae resistant to fluoroquinolones, tetracycline, penicillin and azithromycin or expanded-spectrum cephalosporins .[6] Recent studies have led to the identification of many genes that are responsible for intrinsic resistance to antibiotics of different classes, including β-lactams, fluoroquinolones and aminoglycosides. This was achieved using high-throughput screens of high-density genome mutant libraries that were created by targeted insertion or random transposon mutagenesis in bacteria such as Staphylococcus aureus, Escherichia coli and Pseudomonas Aeruginosa(9,10) The resistance problem encompasses not only bacteria, but also fungal, viral and parasitic diseases.

The message emanating from the shadow epidemic is the same—be aware of resistance and the approaches to curtail it. New diagnostics and new therapeutics and understanding ways to assure delivery of these agents appropriately are needed to help in rapid organism identification and selection and use of effective therapies.

1. General Mechanisms Of Antibiotic Resistance

Dense populations of bacteria resist eradication by drug concentrations considerably greater than those required to kill the same population at a lower density in a phenomenon known as the 'inoculum effect'.[12] One mechanism for density-dependent antibiotic efficacy is drug inactivation by bacterially expressed resistance enzymes . The population's collective capacity to inactivate the drug depends upon several factors, including the number of cells expressing the enzyme conferring resistance.Outer-membrane permeability In bacteria, the cytoplasmic membrane (CM) serves to separate and provide a barrier between the external environment and their cytoplasm.

Due to the lipid bilayer component of biological membranes, they are flexible self-sealing envelopes. The fluidity of a membrane directly impacts the extent of permeability: the more flexible, the more permeable (Vance and Vance, 1996). However, decreasing the permeability of the CM, and thus decreasing the fluidity, would have detrimental effects on the structure and activity of the numerous membrane proteins present within this bilayer. To circumvent this limitation, and as an act of self-preservation, some bacteria assemble additional external structures to serve as a permeability barrier retarding potentially toxic substances.

The thick outer peptidoglycan layer, adorned with teichoic acid polymers and covalently-bound proteins indicative of Gram-positive bacteria, serves more of a structural role in these organisms, providing tensile strength and counteracting the osmotic pressure imparted by the cytoplasm. Antibiotic resistance due to target alterations Antibiotic resistance stemming from alterations in the target(s) of the drugs in such a way as to counter their toxic effects is common in pathogens and non-pathogens. The involvement of PBPS in penicillin resistance has been. Briefly mentioned earlier.

The pbps are trans-peptidases which catalyse the crosslinking reaction between two stem peptides, each linked to adjacent N-acetyl-muramic acid residues of the peptidoglycan backbone. This reac- tion which crosslinks the penultimate D-alanine residue of one peptide (the donor) with the third L-lysine residue of the next peptide (the acceptor) and elimination of the ultimate D-alanine of the donor, is responsible for confer- ring rigidity to the cell wall. Penicillin and other related antibiotics which are structurally similar to the D-ala-D- ala dipeptide form fairly stable covalent complexes with pbps and thereby inhibit the crosslinking reaction, result- ing in the weakening of the cell wall and ultimate lysis of the cell. Many mutational changes in pbps have been shown to result in penicillin resistance. Some of them are: reduction in the affinity of pbps to penicillin, over expression of endogenous, low-affinity PBPS encoding genes, etc. These have been reported and reviewed exten- sively.

2. Mode of Action

The activity of an antibiotic on microorganisms is essentially measured by its minimal inhibitory concentration (MIC), which, although not as accurate as the minimal bactericidal concentration, is easier to measure. For a given antibiotic there is a threshold or a grey zone that separates the bacteria defined as susceptible from those defined as resistant. This threshold is determined by the concentration of antibiotic that can be achieved in the bloodstream when a therapeutic dose is administered. The problem with H. Pylori is that the concentration of antibiotics should be considered in the gastric mucosa and not in the bloodstream. Furthermore, because the ph strongly influences the antimicrobial activity, this value should be taken into account. Such data are difficult, if not impossible, to obtain because the stomach is not easily accessible. It is especially difficult to follow drug kinetics in this organ over a long time period; also, the ph varies during a 24-hour period and is not the same in the different zones where the bacteria live.

The mucosal concentration may also vary between the different areas of the stomach. Attempts to resolve these questions have been made but, in some instances, have led to an erroneous conclusion: it was proposed, for example, that amoxicillin had only a topical activity but was shown later that eradication can be obtained using this drug only in a parenteral treatment. Because of these difficulties, clinical data obtained from carefully designed and conducted trials tend to be the solution in defining the MIC threshold.

3. MDR efflux pumps

Efflux pumps are widespread and present in the chromosome of all organisms (Van, even those that do not produce antibiotics, suggesting they have evolved for purposes other thanavoiding antibiotics. Thefirst example of effluxmediated antibiotic resistance was reported for tetracycline in the 1970s (Ball et al., 1977, 1980; Levy and mcmurry, 1978; mcmurry et al., 1980) and since then, active efflux of a plethora of antibacterial agents has been well documented in many Gram-positive and Gramnegative bacteria. Efflux pumps can either be substrate specific, and only export one molecule, or they can be more broad-spectrum, and export structurally distinct classes of molecules (Piddock, 2006). It has been suggested that antibiotic resistance mediated by active efflux may be a fortuitous by-product of the broad-range substrate specificity exhibited by such pumps; typically efflux pumps transport more than one molecule and they often export toxic molecules that have been produced by the host (Piddock, 2006).

Protein Synthesis Interference: Antibiotics (aminoglycosides, tetracyclines, macrolides, chloramphenicol, fusidic acid, mupirocin, streptogramin, and oxazolidinones) can interfere with protein synthesis at its different stages; for example, during transcription via RNA polymerase, rifamycins modify a specific target . Aminoglycosides (gentamicin, tobramycin, amikacin) bind to the 30S ribosomal subunit while chloramphenicol binds to the 50S ribosomal subunit and suppresses protein synthesis .[13,14]

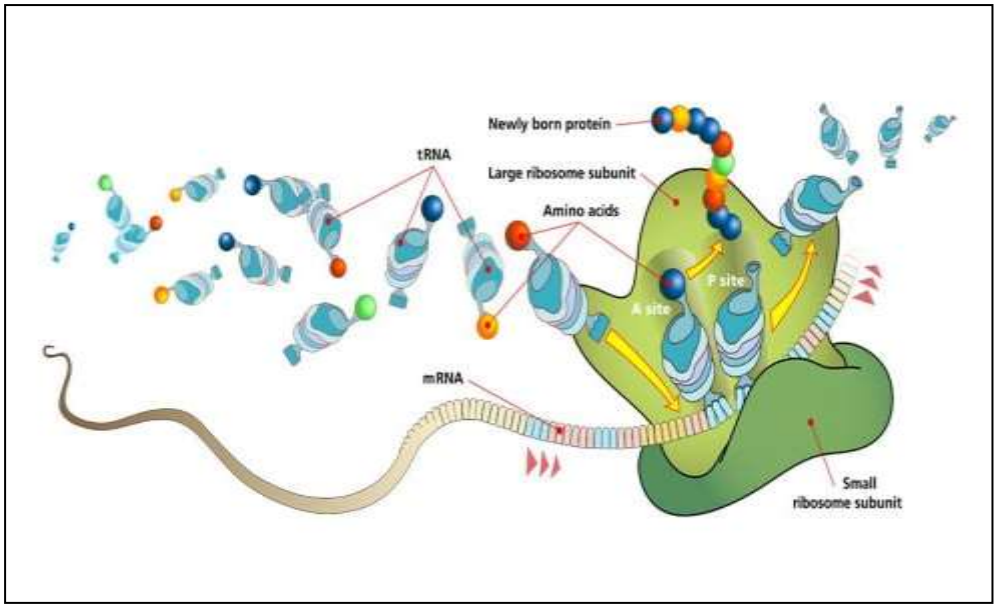

Fig: The process of protein synthesis

Peptidoglycan Structure Alteration. Inhibition of cell wall synthesis is performed by β-lactams, e.g., penicillins, cephalosporins, carbapenems, monobactams, and glycopeptides, e.g., vancomycin and teicoplanin. The presence of mutation in pbps leads to a reduced affinity to β-lactam antibiotics. It results in resistance of E. Faecium to ampicillin and S. Pneumoniae to penicillin. S. Aureus resistance to methicillin and oxacillin is associated with integration of a mobile genetic element – "staphylococcal cassette chromosome mec" into the chromosome of S. Aureus that contains resistance gene meca.

Meca gene encodes PBP2a protein, a new penicillin-binding protein, that is required to change a native staphylococcal PBP (15,16,17). PBP2a shows a high resistance to β-lactam antibiotics (they do not bind to β-lactams) and ensures cell wall synthesis at lethal β-lactam concentrations.

S. Aureus strains resistant to methicillin can be cross resistant to all β-lactam , streptomycin, and tetracycline and in some cases to erythromycin . When lesions in membrane proteins are present, cross-resistance between β-lactam antibiotics and fluoroquinolones possible.(18,19)

4. Resistance to glycopeptides

Since the widespread emergency of MRSA, vancomycin has represented the cornerstone of therapy for MRSA infections. Over the last decade, a long-feared event has occurred: the appearance of strains that are not susceptible to vancomycin, showing either intermediate resistance (vancomycin intermediate S. Aureus [VISA]) or, worse, full resistance to this antibiotic (vancomycin resistant S. Aureus [VRSA]). Two aspects of this occurrence should be noted: first, to date, VISA and VRSA have emerged almost exclusively from MRSA, with few exceptions involving strains with heteroresistance (see below) ; second, resistance does not develop step-wise and VRSA does not progress from VISA, since VISA and VRSA have completely different resistance mechanism [(23,24)]

5. Aminoglycoside:

The aminoglycoside antibiotics are broad-spectrum antibacterial compounds that are used extensively for the treatment of many bacterial infections. In view of the current concerns over the global rise in antibiotic-resistant microorganisms, there has been renewed interest in the mechanisms of resistance to the aminoglycosides, including the superfamily of aminoglycoside-modifying enzymes.

Aminoglycosides constitute a large group of biologically active bacterial secondary metabolites . Although they are best known as antibiotics for the treatment of a variety of diseases, such as tuberculosis and serious nosocomial infections, the aminoglycosides have numerous applications, a few of which are listed in. Here, we will concentrate on the aminoglycoside antibiotics, all of which have the ribosome as the primary target; members of this class have a wide variety of biological activities extend ing to the modulation of the activity of enzymes and ribozymes. Aminoglycoside inhibition of bacterial cell growth occurs by inhibition of one or more of the biochemical steps involved in translation on the ribosome 1. This mechanism of action has been confirmed by the demonstration that point mutations or enzymic modifications in ribosomal components that reduce amino glycoside binding to the ribosome confer high level resistance in bacteria. A significant advance in the understanding of the aminoglycoside-ribosome interaction has been the determination of the 3-D structure of the complex between paromomycin and the A site of 16S ribosomal RNA[23]

Aminoglycoside Structure:

The structure of aminoglycosides consists of a hexose ring, to which various amino sugars are attached via glycosidic linkages. Aminoglycosides can be classified into two main structural classes based on the aminocylitol nucleus: streptidine (streptomycin) and deoxystrepatamine (gentamicin, tobramycin, amikacin, kanamycin, neomycin, and plazomicin) (Figure 6). Irrespective of their structural differences, all aminoglycosides exhibit concentration-dependent bactericidal activity through inhibition of protein synthesis. The structural difference seems to play an important role in escaping the bacterial resistance mechanisms, especially by offering structural robustness against metabolizing enzymes, such as Aminoglycoside Modifying Enzymes (ames), and target-modifying 16S rna methyl transferases (16S-rmtases), produced by the bacteria . Amikacin and plazomicin have been shown to have increased stability against ames compared to gentamicin [5]. All currently marketed aminoglycosides are affected by 16S-rmtases, rendering them inactive against the organisms producing the enzyme .[24]

6. Basics of Antimicrobial Action

The chemical structure required for both potency and the spectrum of antimicrobial activity of aminoglycosides is that of one or several aminated sugars joined in glycosidic linkages to a dibasic cyclitol. In most clinically used aminoglycosides the latter is 2-deoxystreptamine, and it is streptidine in streptomycin and derivatives and fortamine in the fortimicin series . Aminoglycosides act primarily by impairing bacterial protein synthesis through binding to prokaryotic ribosomes.

Passage of these highly polar molecules across the outer membrane of gram-negative bacteria is a selfpromoted uptake process involving the drug-induced disruption of Mg21 bridges between adjacent lipopolysaccharide molecules[25,26]. Penetration through porin channels is unlikely because of the large size of aminoglycosides . Subsequent transport of aminoglycosides across the cytoplasmic (inner) membrane is dependent upon electron transport and is termed energy-dependent phase I.

It is rate limiting and is blocked or inhibited by divalent cations, hyperosmolarity, low ph , and anaerobiosis. In the cytosol, aminoglycosides bind to the 30S subunit of ribosomes, again through an energy-dependent process[27]. While this binding does hynot prevent formation of the initiation complex of peptide synthesis , it perturbs the elongation of the nascent chain by impairing the proofreading process controlling translational accuracy . The aberrant proteins may be inserted into the cell membrane, leading to altered permeability and further stimulation of aminoglycoside transport.

It is the 2-deoxystreptamine and the primed amino sugar which are essential for causing the lack of fidelity in the translation process[23]. The nucleotides responsible for aminoglycoside binding form an asymmetrical internal loop caused by noncanonical base pairs[23]. These key structural features are also found in the rev-binding site of human immunodeficiency virus type 1 (HIV-1) [10], but aminoglycosides are unlikely to become anti-HIV drugs, as was originally hoped, without thorough chemical optimization and/or screening because of their lack of specificity.

7. Conclusion:

This review article focus on safety and efficacy of aminoglycoside in use as antibiotic. As we know antibiotics are widely used in now a days for the treatment of various bacterial infection, hence, development of resistence in one of the most important factor to be consider.

Resistance to aminoglycosides may occur based on several mechanisms enzymatic modification and inactivation of the aminoglycosides, mediated by aminoglycoside acetyltransferases, nucleotidyltransferases, or phosphotransferases and commonly observed across gram-positive and -negative bacteria.

Aminoglycoside has wide spectran activity against gram positive as well as gram negative bacteria. Gentamicin, Amikacin, Tobramycin, Neomycin, and Streptomycin.these are drugs used for antibacterial treatment.

Hence this review consist information of development of resistance toward bacteria, also it consist information to overcome of bacterial resistance.

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