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REVIEW: DIFFERENT BENEFITS OF STREPTOMYCIN AND ITS MECHANISM OF ACTION

[1]Mohammed Ali Alshamrani, [2]Naif Suliman Almahyawi, [3]Doaa Omar Asraf, [4]Khalid Abdullah AlHarbi, [5]Bader Hadi Ali Alyami, [6]ESSA MOHAMMED ALLBDI, [7]Rezan Saeed Al amoudi, [8]Ahmad Hassan Alomari, [9]Majed Mnawer Almutery, [10]Abdulrhman Munawer Almutairi

[1]King abdulaziz Medical city -Western Region, National Guard Jeddah
Pharmacist
[2]National guard hospital, Pharmacy Technician
[3]Supervisor Pharmacy Services, King Abdulaziz Medical city, National Guard Jeddah
[4]Pharmacy Supervisor, King AbdullAziz Medical city - western region
[5]Pharmacist II, King abdulaziz Medical city in jeddah
[6]Technical Pharmacists, Eradah Complex forMental health
[7]Pharma Technician, Eradah Complex for Mental Health
[8]Pharma Technician, Eradah Complex for Mental Health
[9]Pharmacist, Eradah Complex for Mental Health
[10]Pharmacist, King Abdulaziz Airport Health Centre\

Abstract:
Streptomycin was the first aminoglycoside antibiotic discovered, derived from the bacteria Streptomyces griseus. It is now mostly used as part of a multi-drug regimen to treat pulmonary tuberculosis. It also exhibits efficacy against a variety of aerobic gram-negative bacteria. We scan electronic databases for relevant papers on the subject that were published up to 2022. Streptomycin is now mostly used as part of a multi-drug regimen for treating pulmonary tuberculosis. It has extra efficacy against certain aerobic gram-negative bacteria and is still the favored treatment for zoonotic illnesses including plague and tularemia. Although streptomycin has traditionally been the drug of choice treating these infections, gentamicin is now routinely utilized due to its increased availability and data indicating equivalent efficacy to streptomycin.

Corresponding author:
Mohammed Ali Alshamrani,
King abdulaziz medical city -western region,
National guard jeddah
Pharmacist

QR Code

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INTRODUCTION:

The antibiotic streptomycin is an aminoglycoside that was first identified as an isolation of the Streptomyces griseus bacteria. It is the first antibiotic aminoglycoside to be found. Brucellosis, tularemia, plague (Y. pestis), TB (when taken with isoniazid, pyrazinamide, and rifampin), and some cases of endocarditis (when treated with beta-lactam antibiotics) are among the aerobic gram-negative bacterial illnesses that it is typically used to treat. It is not as effective against Pseudomonas aeruginosa as other aminoglycoside antibiotics, such as gentamycin and tobramycin. As antibiotic resistance has grown, the once broad range of effectiveness against both gram-positive and gram-negative bacteria has significantly decreased. It seems that the blockage of its active transport into the bacterial cell is linked to the resistance mechanism. Most Streptococci species and Enterobacteriaceae are commonly resistant bacteria [1,2].

Despite being one of the first and most successful treatments for pulmonary tuberculosis in the past, streptomycin is now mostly used as an alternate therapy, coming in second to the current "RIPE" (rifampin, isoniazid, pyrazinamide, and ethambutol) regimen. Nevertheless, it is nevertheless a potentially useful treatment to consider in situations where RIPE therapy is not available or cannot be tolerated [3] .

In the growing field of treating drug-resistant Mycobacterium tuberculosis infections, where typical combination therapy consisting of rifampin, isoniazid, pyrazinamide, and ethambutol is ineffective, streptomycin becomes very useful. Among other preferred antibiotics that are active against M. tuberculosis, such as rifapentine, rifabutin, linezolid, and several fluoroquinolone antibiotics including levofloxacin, gatifloxacin, and moxifloxacin, streptomycin is regarded as a suitable alternative therapy in these situations [4,5].

DISCUSSION:

The injectable streptidine aminoglycoside antibiotic streptomycin was the first antimicrobial drug to show evidence of efficacy against M. tuberculosis, having been discovered in 1944. First-ever multidrug combination chemotherapy for tuberculosis (TB) used streptomycin along with isoniazid and para-aminosalicylic acid (PAS), which was launched in 1952. Due to the early emergence of streptomycin resistance brought about by its first broad use, its clinical utility was thereafter limited. Up until the 1980s, streptomycin was a necessary part of first-line TB treatment, and until recently, it was advised to use it empirically in retreatment TB regimens [6].

Commercial diagnostic procedures that evaluate for genotypic streptomycin resistance are absent, despite the fact that the bulk of the molecular determinants of aminoglycoside resistance are known. Extensively drug-resistant (XDR) tuberculosis (TB) is characterized by multidrug-resistant (MDR) isolates that also have resistance to quinolones and other injectable drugs (kanamycin, amikacin) [7]. Streptomycin resistance is not a part of this description. Currently, streptomycin is categorized as a group C second-line drug that should only be used in specific situations as part of lengthier MDR-TB regimens. Even while second-line injectable medications usually cause XDR isolates to become cross-resistant, there may be unrealized potential for sustained streptomycin use to treat low-level resistance [6, 7].

Streptomycin is bactericidal and interferes with ribosomal peptide/protein synthesis, just like all aminoglycosides do. By attaching itself to a side of 16S rRNA on the smaller 30S component of the bacterial ribosome, it prevents the bacterial ribosome from functioning properly and stops the production of new peptide bonds, which stops further protein synthesis. Being hydrophilic, aminoglycosides are unable to pass through the hydrophobic bacterial cell membrane. Aminoglycosides are only effective against aerobic bacteria because they require an electron transport mechanism that is utilized during the respiratory cycle of the organism to do this [8,9].

Since streptomycin is poorly absorbed in the gastrointestinal system, it is usually injected deeply into the muscle to be delivered parenterally. On the other hand, those who have insufficient muscle mass or who need several dosages may develop an intolerance to injections due to pain. An alternate mode of delivery in some situations may be intravenous. Streptomycin has a half-life of roughly 2.5 hours in the blood, and its peak concentration in the serum is around 50 mg/ml. Aminoglycosides are primarily found in lean tissue. Therefore, rather than basing dosage on total body weight, obese patients' dosage should be determined by their desired body weight [1,8]. Young adults are usually treated with 1g per day, given either as a single dosage or divided into two doses, while receiving IM and IV treatment. However, a lowered dose of 0.75g/day is administered to persons over 40. Children should not take more than 20 mg/kg per day and should never exceed 40 mg/kg [3].

Aminoglycosides have a core structure of amino sugars linked by glycosidic connections to a dibasic aminocyclitol, which is usually 2-deoxystreptamine [10]. Based on the identity of the aminocyclitol moiety, aminoglycosides are divided into four subclasses: (1) no deoxystreptamine (e.g., streptomycin, which has a streptidine ring); (2) a mono-substituted deoxystreptamine ring (e.g., apramycin); (3) a 4,5-di-substituted deoxystreptamine ring (e.g., neomycin, ribostamycin); or (4) a 4,6-di-substituted deoxystreptamine ring (e.g., gentamicin, amikacin, tobramycin, and plazomicin). **Figure 1** [11] depicts examples of each subclass. The basic structure is embellished with a range of amino and hydroxyl substitutions, which have a direct impact on the modes of action and sensitivity to various aminoglycoside-modifying enzymes (AMEs) associated with each aminoglycoside.

Aminoglycoside entrance into bacterial cells occurs in three steps, the first of which enhances bacterial membrane permeability, while the second and third are energy-dependent. The first stage involves electrostatic binding of the polycationic aminoglycoside to negatively charged bacterial membrane components such as phospholipids and teichoic acids in Gram-positive organisms and phospholipids and lipopolysaccharide (LPS) in Gram-negative organisms, followed by magnesium ion displacement [12]. These cations are crucial for the cross-bridging and stabilization of the lipid components of the bacterial membrane, and their removal causes the outer membrane to rupture, increased permeability, and the commencement of aminoglycoside uptake [12]. This phenomenon promotes cytoplasmic entrance via a gradual, energy-dependent, electron-transport-mediated mechanism. When aminoglycoside molecules enter the cytoplasm, they inhibit protein synthesis and cause protein mistranslation. These mistranslated proteins insert into and disrupt the cytoplasmic membrane, allowing aminoglycosides to enter [13]. This causes rapid uptake of more aminoglycoside molecules into the cytoplasm, increasing inhibition of protein synthesis, mistranslation, and cell death [13].

Monitoring for streptomycin toxicity is especially necessary in children and patients with renal impairment, as streptomycin is absorbed through the glomerulus. Renal impairment might increase the half-life of the medication by 50 to 100 hours. Streptomycin toxicity is commonly assumed to be characterized by ototoxicity and vestibular dysfunction. Ototoxicity can cause deafness in extreme circumstances, thus use caution when taking streptomycin with other potentially ototoxic medications. Vestibular impairment frequently appears during treatment and is usually permanent. Streptomycin has the potential to be nephrotoxic as well. modest proteinuria, increased cellular excretion, and modest increases in blood urea will result. Unlike ototoxicity, nephrotoxicity is usually only temporary. There have also been instances of neuromuscular blockade with streptomycin use in conjunction with body cavity installation, use under anesthesia with the use of neuromuscular blocking drugs, and overdose in youngsters. Optic nerve dysfunction, peripheral neuritis, and encephalopathy can all result from neurotoxic consequences. Intrathecal usage, albeit uncommon, has been linked to arachnoiditis. Dialysis can lower serum streptomycin concentrations in cases of medication toxicity [9,13].

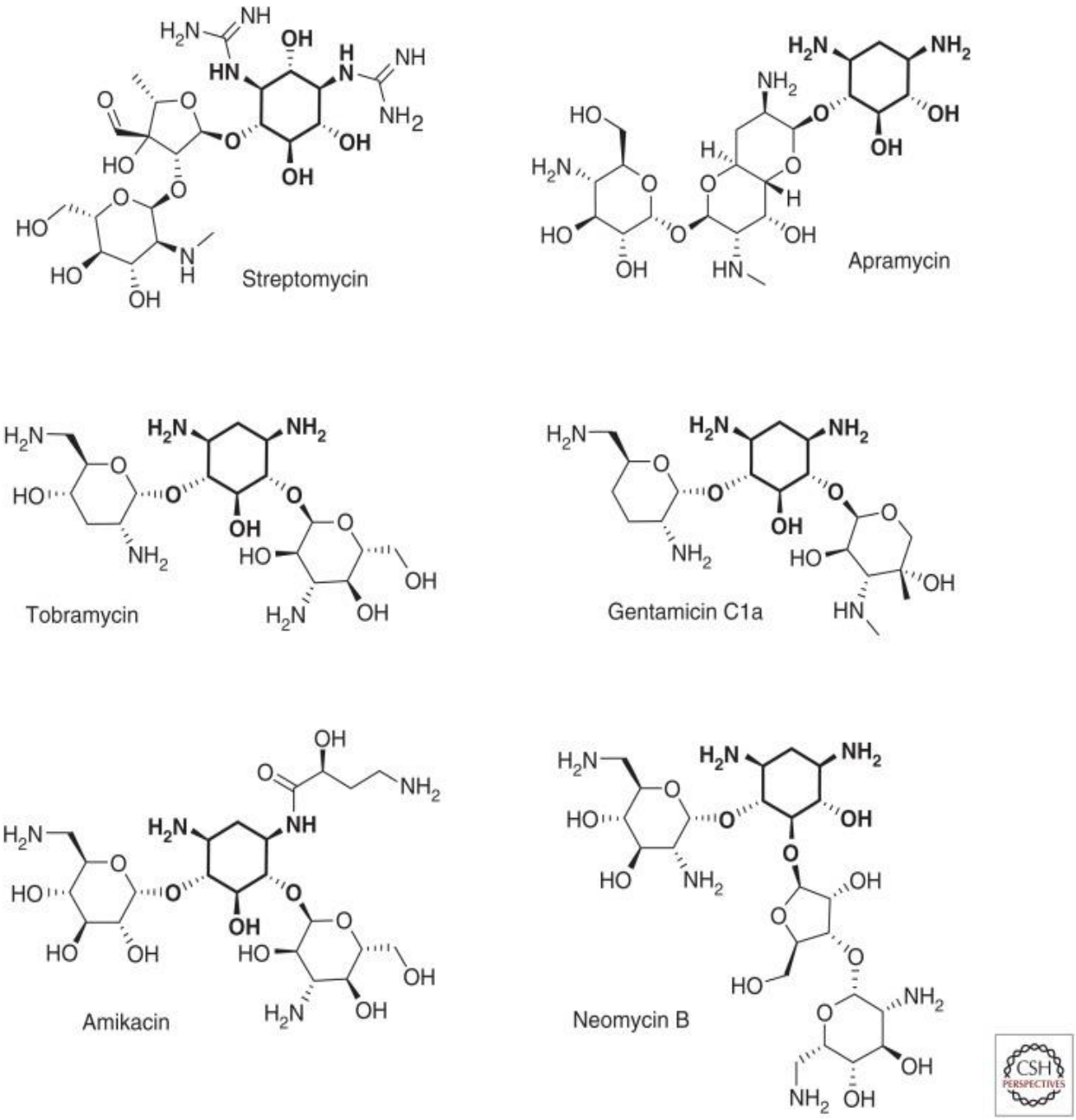

Figure 1: Structures of representative aminoglycosides, including the atypical aminoglycosides streptomycin and apramycin

Aminoglycosides are effective against both Gram-positive and Gram-negative bacteria. Aminoglycosides are especially effective against Enterobacteriaceae members such as E. coli, Klebsiella pneumoniae and K. oxytoca, Enterobacter cloacae and E. aerogenes, Providencia spp., Proteus spp., Morganella spp., and Serratia spp. [14]. Furthermore, aminoglycosides are effective against the causative agents of plague and tularemia, Yersinia pestis and Francisella tularensis, respectively. Staphylococcus aureus, including methicillin-resistant and vancomycin-intermediate and -resistant isolates, Pseudomonas aeruginosa, and, to a lesser extent, Acinetobacter baumannii, are also susceptible. Mycobacterium TB, Mycobacterium fortuitum, Mycobacterium chelonae, and Mycobacterium avium are all susceptible to aminoglycosides. [15].

Because active electron transport is necessary for aminoglycoside absorption into cells, the class is dormant against anaerobic bacteria. Aminoglycosides are similarly ineffective against the majority of Burkholderia spp., Stenotrophomonas spp., Streptococcus spp., and Enterococcus spp. [16,17].

Streptomycin Rresistance:

Streptomycin resistance manifests itself in a variety of ways, including enzymatic modification, target site alteration via an enzyme or chromosomal mutation, and efflux. Each of these mechanisms affects various members of the class differently, and many mechanisms are frequently involved in any given resistant isolate. Resistance to aminoglycosides through target site mutations has not been found since, with the exception of Mycobacterium spp. and Borrelia spp., practically all prokaryotes encode multiple copies of rRNA. Although current large-scale monitoring systems provide insight into phenotypic aminoglycoside resistance among key pathogens, these studies have not traditionally focused on the epidemiology of specific resistance mechanisms [18,19].

CONCLUSION:

Streptomycin is an antibiotic in the aminoglycoside class. It operates by attaching permanently to the bacterial ribosome, specifically the 30S subunit. This binding limits protein synthesis, preventing bacteria from generating required proteins for survival. Streptomycin effectively kills or slows the growth of a wide spectrum of gram-negative and certain gram-positive bacteria by affecting bacterial protein synthesis.

The discovery of streptomycin and its subsequent application in the treatment of bacterial infections transformed medicine. It paved the path for the creation of countless additional antibiotics and heralded a new era in the management of infectious diseases. The success of streptomycin prompted scientists to investigate and discover new antibiotics, resulting in the invention of medications such as penicillin, tetracycline, and erythromycin. Streptomycin has had a major impact on worldwide public health, as it continues to save lives and improve results in the treatment of numerous bacterial diseases.

Streptomycin is regarded as a watershed moment in medical history, as it provides an effective treatment option for a wide spectrum of bacterial infections. Its discovery and subsequent usage altered the course of infectious disease management, emphasizing the significance of antibiotic stewardship in preventing the formation of drug-resistant bacteria and preserving the efficacy of this priceless medicine.

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