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REVIEW ARTICLE

A Review on the Discovery, Pharmacology, and Clinical Significance of Streptomycin

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Abstract: Streptomycin, isolated in 1943 from the actinobacterium *Streptomyces griseus*, was the first aminoglycoside antibiotic discovered and regarded as a landmark in modern medicine. Its introduction provided the first effective chemotherapy against Mycobacterium tuberculosis, revolutionizing the treatment of tuberculosis. The molecule is a bactericidal agent that functions by irreversibly binding to the 16S rRNA of the bacterial 30S ribosomal subunit. This binding interferes with translational initiation and promotes the misreading of mRNA, leading to the synthesis of non-functional proteins that disrupt cell membrane integrity. Pharmacokinetically, streptomycin is a highly polar molecule, resulting in negligible gastrointestinal absorption and necessitating parenteral administration. It distributes primarily within the extracellular fluid and is eliminated unchanged via glomerular filtration. Its clinical utility is concentration-dependent and benefits from a significant post-antibiotic effect. Despite its historical importance, systemic use is now limited by significant toxicities, primarily irreversible ototoxicity and reversible nephrotoxicity. Today, streptomycin retains a critical, specialized role in combination therapy for multidrug-resistant tuberculosis, specific zoonotic infections such as plague and tularemia, and in synergistic regimens for bacterial endocarditis.

Keywords: Streptomycin; Aminoglycoside; *Streptomyces griseus*; Tuberculosis; 30S Ribosomal Subunit; Ototoxicity

1. Introduction

The discovery of streptomycin in 1943 marked a pivotal moment in the history of medicine and the dawn of the antibiotic era for Gram-negative bacteria and mycobacteria [1]. Isolated from the soil actinomycete *Streptomyces griseus* by Albert Schatz, a graduate student in Selman Waksman's laboratory, streptomycin rapidly proved its efficacy [2]. Its most profound impact was as the first antimicrobial agent effective against *Mycobacterium tuberculosis*, transforming tuberculosis from an intractable disease with high mortality into a treatable condition [3]. This discovery, which earned Waksman the Nobel Prize in 1952, established a new class of antibiotics—the aminoglycosides—and spurred the search for other therapeutic agents from microbial sources [4].

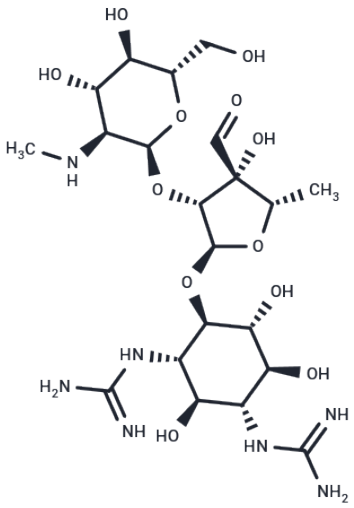

Figure 1. Structure of Streptomycin

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Streptomycin is a trisaccharide composed of streptidine, streptose, and N-methyl-L-glucosamine [5]. Chemically, its IUPAC name is 5-(2,4-diguanidino-3,5,6-trihydroxy-cyclohexoxy)-4-[4,5-dihydroxy-6-(hydroxymethyl)-3-methylamino-tetrahydropyran-2-yl]oxy-3-hydroxy-2-methyl-tetrahydrofuran-3-carbaldehyde. As a polycationic base, it is highly polar and water-soluble. These properties are fundamental to its pharmacokinetic profile, dictating its route of administration, distribution in the body, and mechanism of entry into bacterial cells [6]. It is typically formulated as streptomycin sulfate for clinical use.

2. Mechanism of Action

Streptomycin's bactericidal effect is a multi-stage process involving entry into the bacterial cell and subsequent inhibition of protein synthesis.

2.1. Bacterial Cell Entry

Entry into Gram-negative bacteria is a complex, energy-dependent process [7]. It begins with an initial, rapid phase where the polycationic streptomycin molecule electrostatically binds to negatively charged components of the bacterial outer membrane, such as lipopolysaccharide (LPS) [8]. This binding displaces divalent cations (Mg^{2+} and Ca^{2+}) that normally stabilize the LPS, leading to membrane disruption and increased permeability [9]. This allows the drug to traverse the outer membrane and access the periplasmic space.

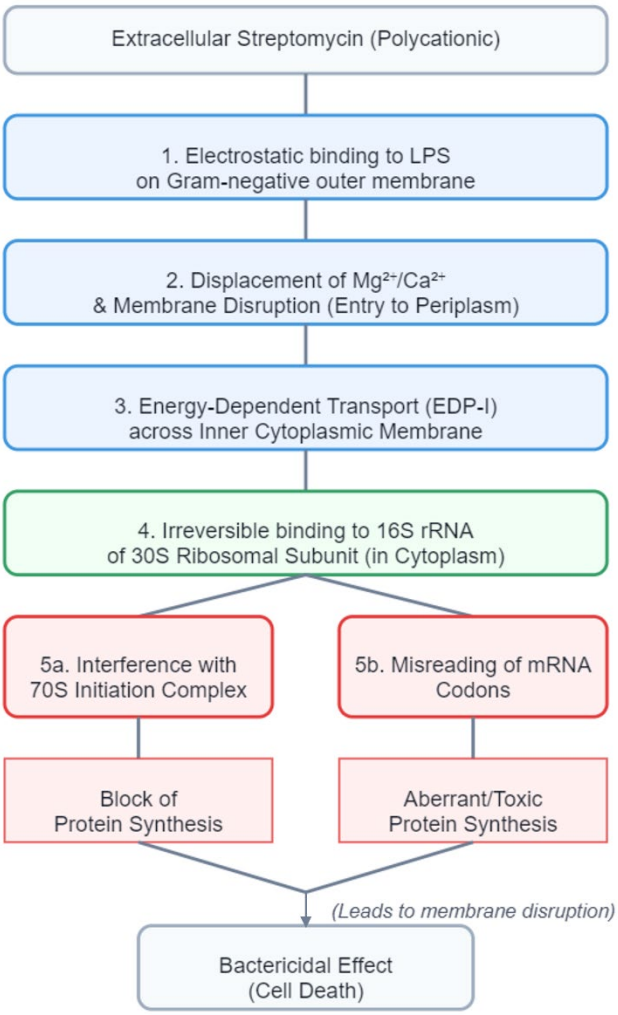

Figure 2. Mechanism of Action of Streptomycin

Subsequent transport across the inner cytoplasmic membrane is biphasic. It involves a slow, energy-dependent phase I (EDP-I), followed by a more rapid, accelerated energy-dependent phase II (EDP-II) [10]. This transport is coupled to the bacterial electron transport chain, which is why aminoglycosides are largely ineffective against anaerobic bacteria that lack this system [11].

2.2. Ribosomal Inhibition

Once in the cytoplasm, streptomycin's primary target is the bacterial 30S ribosomal subunit. It binds irreversibly to a specific site on the 16S rRNA, near the A-site (aminoacyl-tRNA binding site) [12]. This binding has two major consequences. First, it interferes with the formation of the 70S initiation complex, effectively blocking the start of protein synthesis [13]. Second, it induces a conformational change in the A-site, causing the misreading of mRNA codons. This leads to the incorporation of incorrect amino acids into the growing polypeptide chain [14]. The accumulation of these mistranslated, aberrant proteins, many of which may be inserted into the cell membrane, leads to further disruption of membrane integrity, loss of essential metabolites, and ultimately, cell death [15]. This multi-pronged attack—blocking initiation and inducing toxic protein synthesis—accounts for streptomycin's potent bactericidal activity.

3. Pharmacological Profile

3.1. Pharmacokinetics

The pharmacokinetic properties of streptomycin are dictated by its high polarity.

3.1.1. Absorption

Gastrointestinal absorption of streptomycin is negligible (less than 1%) [16]. Consequently, for systemic infections, it must be administered parenterally, typically via intramuscular (IM) injection, from which it is rapidly and completely absorbed. Intravenous (IV) administration is also possible.

3.1.2. Distribution

Following absorption, streptomycin distributes primarily into the extracellular fluid compartment. Its volume of distribution is low, approximately 0.2 to 0.3 L/kg in adults, reflecting its poor lipid solubility and limited tissue penetration [17]. It does not readily cross the blood-brain barrier, resulting in low concentrations in the cerebrospinal fluid (CSF), even in the presence of meningeal inflammation [18]. It also penetrates poorly into vitreous humor, bronchial secretions, and abscesses. However, it does cross the placenta and can accumulate in fetal plasma and amniotic fluid [19]. Plasma protein binding is relatively low, typically reported in the range of 20-35%.

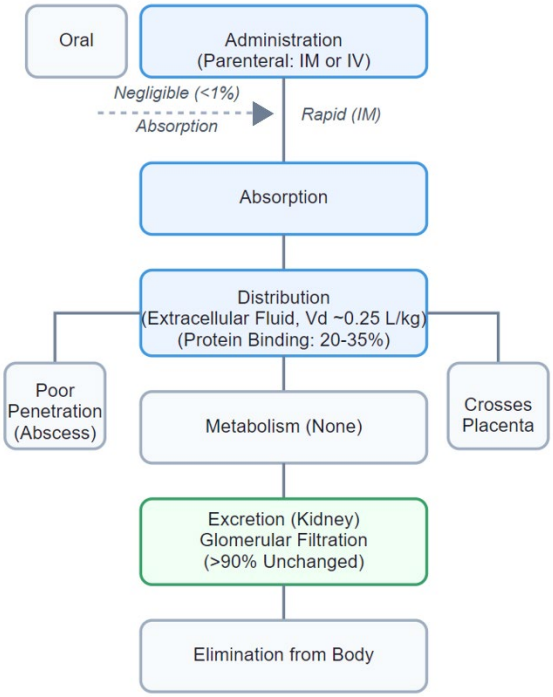

Figure 3. Pharmacokinetic Profile of Streptomycin

3.1.3. Metabolism and Excretion

Streptomycin is not metabolized in the body [20]. It is eliminated almost entirely by the kidneys via glomerular filtration, with over 90% of a dose excreted unchanged in the urine within 24 hours in patients with normal renal function [21]. The serum half-life is approximately 2.5 hours in healthy adults. This reliance on renal excretion means that the half-life is significantly prolonged in patients with renal impairment, necessitating careful dose adjustments to prevent accumulation and toxicity [22].

Table 1. Pharmacokinetic Parameters of Streptomycin

Parameter	Value / Description
Bioavailability (Oral)	< 1% (Negligible)
Bioavailability (IM)	~100% (Rapid and complete absorption)
Volume of Distribution (Vd)	0.2 – 0.3 L/kg (Confined to extracellular fluid)
Plasma Protein Binding	20% – 35%
Metabolism	Not metabolized
Elimination Half-life	~2.5 hours (in adults with normal renal function)
Excretion	>90% eliminated unchanged in urine via glomerular filtration

3.2. Pharmacodynamics

Streptomycin exhibits concentration-dependent bactericidal activity, meaning that higher peak concentrations (Cmax) relative to the minimum inhibitory concentration (MIC) correlate with a more rapid and extensive bacterial killing [23]. It also possesses a significant post-antibiotic effect (PAE), where bacterial growth remains suppressed for a period even after the serum concentration has fallen below the MIC [24]. These two principles—concentration-dependent killing and a long PAE—are the pharmacological basis for modern, high-dose, extended-interval (once-daily) dosing regimens. Such regimens maximize efficacy while minimizing the time drug concentrations are in the toxic range, potentially reducing the risk of nephrotoxicity [25].

4. Clinical Applications

The clinical use of streptomycin has evolved significantly since its introduction. Once a broad-spectrum agent, its application is now highly specialized due to the availability of less toxic alternatives and the rise of bacterial resistance.

4.1. Tuberculosis

Streptomycin's historical role as a first-line agent for tuberculosis has been largely superseded. However, it remains a critical component of second-line treatment regimens for multidrug-resistant tuberculosis (MDR-TB), always used in combination with other active agents to prevent the emergence of resistance [26].

Table 2. Major Clinical Applications of Streptomycin

Indication	Role of Streptomycin	Regimen
Multidrug-Resistant Tuberculosis (MDR-TB)	Second-line agent	Always used in a multi-drug combination regimen.
Plague (*Yersinia pestis*)	First-line agent	A primary treatment for all forms of plague.
Tularemia (*Francisella tularensis*)	First-line agent	Highly effective, considered a drug of choice.
Brucellosis	Combination therapy	Used synergistically, typically with doxycycline.
Bacterial Endocarditis	Synergistic agent	Combined with a cell-wall agent (e.g., penicillin) for enterococcal or resistant viridans streptococcal infections.

4.2. Non-Tuberculous Infections

Streptomycin retains first-line status for several severe, uncommon infections. It is a cornerstone of therapy for plague, caused by *Yersinia pestis* [27], and tularemia, caused by *Francisella tularensis* [28]. It is also used in combination with doxycycline for the treatment of brucellosis [29].

Its use in synergistic combinations is also important. For bacterial endocarditis, particularly cases involving *Enterococcus faecalis* or resistant viridans group streptococci, streptomycin is combined with a cell-wall active agent (such as penicillin G or ampicillin) [30]. The cell-wall agent inhibits peptidoglycan synthesis, which is thought to enhance the uptake of streptomycin into the bacterial cell, leading to a synergistic bactericidal effect where neither agent alone would be sufficient [31].

4.3. Non-Clinical Use

A common application of streptomycin is in biomedical research. It is frequently formulated with penicillin as "Pen-Strep," a standard antibiotic cocktail added to eukaryotic cell culture media to prevent bacterial contamination, which can otherwise confound experimental results [32].

5. Adverse Effects and Toxicity

The therapeutic utility of streptomycin is significantly limited by its potential for severe, dose-dependent toxicities.

5.1. Ototoxicity

Ototoxicity is the most serious and feared adverse effect, as it is often irreversible [33]. Streptomycin primarily causes vestibular toxicity (vestibulotoxicity), damaging the sensory hair cells of the vestibular apparatus. This manifests as vertigo, nausea, vomiting, and ataxia (loss of balance) [34]. Cochlear toxicity, leading to tinnitus and high-frequency hearing loss, can also occur but is less common than with other aminoglycosides like amikacin or kanamycin. The risk is related to cumulative dose, duration of therapy, peak and trough concentrations, and pre-existing renal impairment [35].

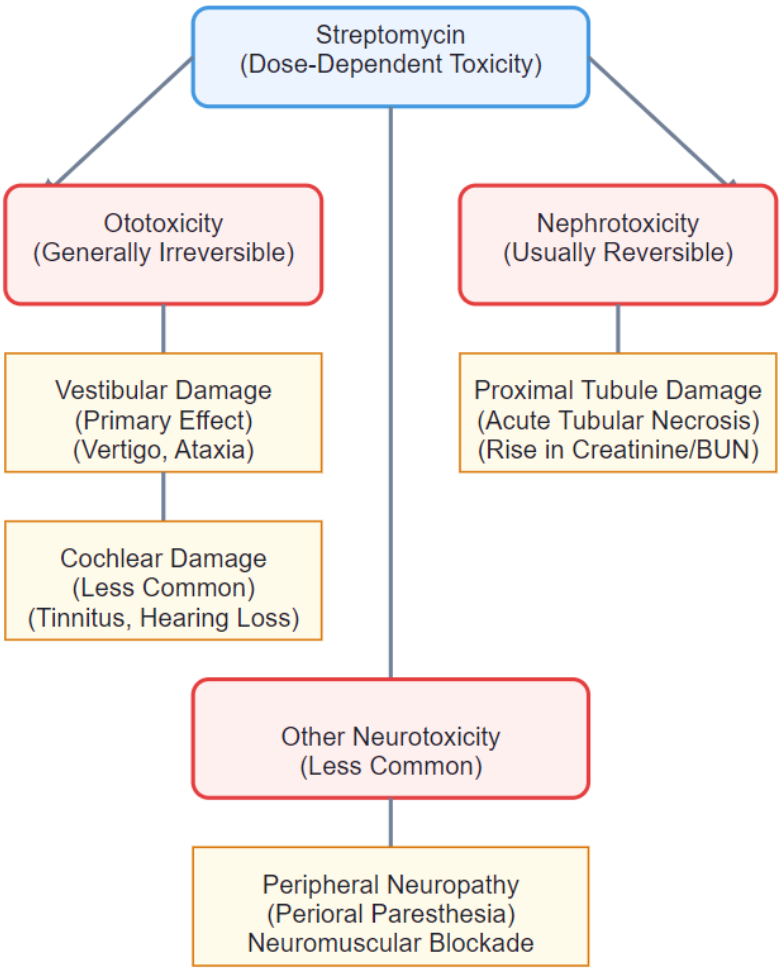

Figure 4. Toxicity of Streptomycin

5.2. Nephrotoxicity

Streptomycin can cause nephrotoxicity by accumulating in the epithelial cells of the renal proximal tubule, inducing acute tubular necrosis (ATN) [36]. This typically presents as a non-oliguric rise in serum creatinine and blood urea nitrogen (BUN) after several days of therapy. Unlike ototoxicity, this effect is usually reversible upon discontinuation of the drug, as the proximal tubule cells have a high capacity for regeneration [37].

5.3. Other Adverse Effects

Neurotoxicity, though less common, can manifest as a peripheral neuropathy (numbness or tingling, particularly around the face) [38]. A rare but serious effect is neuromuscular blockade, which can lead to respiratory paralysis. This is typically seen in patients with co-administering neuromuscular blocking agents or in those with conditions like myasthenia gravis [39]. Hypersensitivity reactions, including skin rash, fever, and eosinophilia, may also occur [40].

Table 3. Adverse Effects and Toxicities

Toxicity Type	Manifestation	Mechanism	Reversibility
Ototoxicity	Vestibular: Vertigo, ataxia, nausea Cochlear: Tinnitus, hearing loss (less common)	Damage to sensory hair cells in the vestibular apparatus and cochlea.	Generally Irreversible
Nephrotoxicity	Non-oliguric rise in serum creatinine and BUN	Accumulation in proximal tubule cells, leading to acute tubular necrosis (ATN).	Usually Reversible
Neurotoxicity	Peripheral neuropathy (paresthesia, especially perioral)	Not fully elucidated; direct neural effect.	Variable
Neuromuscular Blockade	Respiratory paralysis, muscle weakness	Inhibition of acetylcholine release at the neuromuscular junction.	Reversible (with intervention)

5.4. Drug Interactions and Contraindications

Careful consideration of potential interactions is essential when administering streptomycin. The most significant interactions involve additive toxicity. Co-administration with other agents that have ototoxic or nephrotoxic potential, such as loop diuretics (e.g., furosemide, ethacrynic acid), amphotericin B, vancomycin, or cisplatin, can dramatically increase the risk of toxicity [41, 42]. The combination with loop diuretics is particularly hazardous, as these drugs can independently cause ototoxicity and also alter fluid and electrolyte balance, exacerbating aminoglycoside toxicity.

Streptomycin is contraindicated in patients with a known history of hypersensitivity or serious toxic reactions to it or any other aminoglycoside, as cross-sensitivity within the class is common [43]. Its use during pregnancy is also contraindicated. Streptomycin readily crosses the placenta and has been definitively linked to bilateral congenital deafness and vestibular damage in the fetus, making it a known human teratogen [44].

Table 4. Clinically Significant Drug Interactions

Interacting Agent / Class	Potential Effects	Recommendation
Loop Diuretics (e.g., Furosemide, Ethacrynic Acid)	Potentiates ototoxicity and nephrotoxicity.	Avoid co-administration if possible. Monitor auditory and renal function closely.
Other Nephrotoxic Agents (e.g., Amphotericin B, Vancomycin, Cisplatin, other Aminoglycosides)	Additive nephrotoxicity.	Avoid concurrent use. If unavoidable, requires intensive monitoring of renal function.
Neuromuscular Blocking Agents (e.g., Succinylcholine)	Potentiation of neuromuscular blockade, risk of respiratory paralysis.	Use with extreme caution, particularly post-operatively. Monitor respiratory status.

6. Conclusion

Streptomycin occupies a unique place in the history of chemotherapy. It saved countless lives and fundamentally altered the course of infectious diseases. While its broad clinical use has been curtailed by the development of safer, more effective antibiotics and the significant, persistent risk of irreversible ototoxicity and nephrotoxicity, it is not obsolete. It remains an indispensable tool in the modern therapeutic arsenal for specific, life-threatening conditions, including multidrug-resistant tuberculosis, plague, tularemia, and synergistic treatment of endocarditis. The continued, careful use of streptomycin requires rigorous patient selection, therapeutic

drug monitoring, and a profound respect for its toxic potential, embodying the critical balance between efficacy and safety that defines modern pharmacotherapy

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