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Original Article

# GENTAMICIN : MYTHS AND TRUTHS

Muralee Mohan[1], Deepthi Shetty[2], Tripthi Shetty[3] & Suman Banerjee[4]
[1]Professor, [2,3]Assistant Professors, [4]Post Graduate, Department of Oral & Maxillofacial Surgery,
A.B. Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India.

Correspondence :
Suman Banerjee
Post Graduate, Department of Oral & Maxillofacial Surgery, A.B. Shetty Memorial Institute of Dental Sciences,
Nitte University, Mangalore - 575 018, Karnataka, India.
E-mail : drsumanbanerjee.surgeon@gmail.com

Abstract :
Gentamicin belongs to the group of antimicrobial agents, aminoglycosides. It is the prototype member of this group of antimicrobial agents that is utilized to treat various bacterial infections, mostly those caused by Gram negative bacteria. This is due to its irreversible binding to the 30S component of the ribosome. But the use of aminoglycosides and thus Gentamicin is limited owing to its profound adverse effects on the ear & the kidney. But proper calculation of the dosage can limit these side effects and prove to be an effective antimicrobial agent.

Keywords: Gentamicin, Dosage, nephrotoxicity

## Introduction :

Aminoglycosides, as the name implies contain amino sugars linked with an aminocyclitol ring by glycosidic bonds. They are poly-cations, and their polarity is responsible for the pharmacokinetic properties shared by all members of the group. None of these drugs is adequately absorbed after oral administration, inadequate concentrations are found in cerebrospinal fluid, and are all excreted relatively rapidly by the normal kidney.

Gentamicin is a broad spectrum antibiotic derived from the species of actinomycete *Micromonospora.* It was first studied and described by Weinstein and co-workers in 1963; isolated, purified and characterized by Roselot et al. It has a broader spectrum of activity than Kanamycin and is currently widely used.

## Mechanism of action

Gentamicin, like all other aminoglycosides, diffuses through the aqueous channels produced by porins in the outer membrane of gram negative bacteria and enters the periplasmic space. It is then transferred into the inner membrane which is dependent on the electron transport. This phase of transport is energy dependent. It is rate limiting and is blocked or inhibited by divalent cations, hyperosmolarity, reduction in pH and anerobiasis. The reduction in pH and anerobiasis results in impairment of the ability to maintain the driving force necessary for transport. Following transport through the cytoplasmic membrane, it binds to polysomes and thus inhibits protein synthesis. This process subsequently accelerates the transport of the antibiotic. This phase is termed as energy dependent phase II. This is in some way related to the disruption of the structure of the cytoplasmic membrane.

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The primary intracellular site of action of aminoglycosides is the 30S ribosomal subunit, which consists of 21 proteins and a single 16S molecule of RNA. It disrupts the normal cycle of ribosomal function by interfering at least in part, with the initiation of protein synthesis, leading to accumulation of abnormal initiation complexes. It also causes misreading of the mRNA template. Thus, incorrect amino acids are incorporated into the growing polypeptide chains.

## Antibacterial activity :

Gentamicin has little activity against anaerobic microbes under anaerobic conditions. Its action against most gram positive bacteria is limited. *Streptococcus pneumonia* and

*Streptococcus pyogenes* are highly resistant. Gentamicin is added to blood agar plates to aid in isolation of these microbes from sputum and pharyngeal secretions. It is active against sensitive strains of enterococci and streptococci at concentrations that can be achieved clinically only when combined with Penicillin. Such combinations result in a more rapid bactericidal effect than is produced by either drug alone. Gentamicin is active against more than 90% strains of *Staphylococcus aureus* and 75% strains of *Staphylococcus epidermidis.* However resistance is mediated by conjugatively transferable plasmids that code for aminoglycoside – modifying enzymes.

Since sensitive microbes are defined as those inhibited by concentrations that can be achieved clinically in plasma without a high incidence of toxicity, the therapeutic peak values are 4- 8 microgram/ml. *Pseudomonas aeruginosa* is more resistant to gentamicin because of plasmid-mediated inactivating enzymes.

Absorption

Gentamicin, being a highly polar cation, is poorly absorbed in the gastrointestinal tract. A very minute concentration (less than 1%) of the dose is absorbed following oral or rectal administration. Its absorption may be increased by gastrointestinal disease. It is absorbed rapidly from intramuscular sites. Peak concentrations occur after 30 to 90 minutes. In critically ill patients, absorption of the drug may be reduced from the intramuscular sites due to poor perfusion.

Distribution

Because of its polar nature, Gentamicin is largely excreted from most cells, the CNS and the eye. The apparent volume of distribution is 25% of the lean body weight and approximates the volume of extracellular fluid. Concentration of gentamicin in the secretions is relatively low. High concentrations are found in the renal cortex and the endolymph and the perilymph of the inner ear. Concentration in bile approaches 30% of those in plasma due to active hepatic secretion. But this represents a minor route of excretion. Concentration in the CSF is less than 10% of plasma in the absence of inflammation and this value may approach 20% in meningitis. Thus, this concentration is inadequate for treatment of gram negative bacillary meningitis in adults.

Elimination

Gentamicin is excreted almost entirely by glomerular filtration and concentration in the urine of 50 to 200 micrograms/ml may be achieved. A large fraction of the parenterally administered dose is excreted unchanged during the first 24 hours with most of it appearing during the first 12 hours. Renal clearance of gentamicin is approximately 2/3rds of the simultaneous creatinine clearance. This observation suggests tubular reabsorption.

Since the elimination of Gentamicin is entirely dependent on the kidney, a linear relationship exists between the concentration of creatinine in plasma and the half life of the drug in patients with moderately compromised renal function. In anephric patients, the half life varies from 20-40 times that determined in normal individuals. Since the nephrotoxicity and ototoxicity are related to the concentration and accumulation of the drug, it is critical to reduce the maintenance dosage in patients with impaired renal function. This must be done with precision as the concentration in plasma that is associated with toxicity is not much greater than that required for the treatment of many bacterial infections. The dose and the time interval between the doses may need alteration. The most consistent plasma concentrations are achieved when the loading dose is given in milligrams per kilogram body weight and since it is minimally distributed in fatty tissue, the lean or the expected body weight should be used.

Adverse effects

Ototoxicity: As these drugs are concentrated in the labyrinthine fluid and are slowly removed when plasma concentration falls, prescribing Gentamicin needs to be carefully done. It primarily affects the vestibular and cochlear part of the ear. The vestibular and cochlear sensory cells/ hairs undergo concentration dependent destructive changes. Cochlear damage starts from the base and spreads to the apex. Hearing loss affects the high

frequency sound first and progressively encompasses lower frequencies. No regeneration of the sensory cells occurs and nerve fibres degenerate in a retrograde manner. Older patients are more susceptible. Tinnitus develops progressively followed by progressive hearing loss.

Vestibular toxicity: Headache is generally accompanied by nausea, vomiting, nystagmus, vertigo, ataxia. If the drug is stopped at this stage, it enters into a chronic stage lasting for 6- 10 weeks when the patient has difficulty only while walking. Compensation by visual and proprioceptive positioning and recovery occurs over 1 – 2 years.

Nephrotoxicity: It manifests as tubular damage resulting in loss of urinary concentrating power, low glomerular filtration rate, nitrogen retention, albuminuria & casts. Toxicity is related to the total amount of drug received by the patient. However, renal damage due to gentamicin & other aminoglycosides is totally reversible, provided the drug is stopped immediately. It has been suggested that gentamicin interferes with the production of prostaglandins. Aminoglycoside induced toxicity can lead to reduced clearance of the drug from the blood which leads to enhanced ototoxicity. 2

A combination of aminiglycosides with cephalosporin or frusemide is likely to induce a lesion.3

Neuromuscular blockade: Gentamicin, like all aminoglycosides, reduces acetylcholine release from motor nerve endings and thus interfere with mobilization of centrally located synaptic vesicles to fuse with the terminal membrane. Its propensity is lesser compared to Neomycin & Streptomycin.

Precautions and interactions:

- To be avoided in pregnancy: risk of fetal ototoxicity
- To be avoided with other ototoxic drugs: high ceiling diuretics, minocycline
- To be avoided with other nephrotoxic drugs e.g. Amphotericin B, vancomycin, cisplatin
- Cautious use in patients past middle age
- Cautious use with muscle relaxants
- Do not mix it with any other drug in the same syringe 2

Antimicrobial spectrum :

Gentamicin is active against most Gram negative bacilli, including *Pseudomonas aeruginosa*. It is also active against penicillinase- resistant staphylococci but inactive against anaerobes and Streptococci with the exception of *Enterococcus faecalis*. In serious infections with this bacterium, Gentamicin may be combined with ampicillin. The dose of gentamicin depends on the renal function, the age and the weight of the patient. In most infections, it is used in the concentration of 5 mg/kg body weight per 24 hours in divided doses, usually every 8 hours. Upto 7.5 mg/kg body weight may be required for serious infections and in neonates. For uncomplicated urinary tract infections, synergistic therapy with penicillin for streptococcal endocarditis, 2 mg/kg weight is generally sufficient. Serum concentrations of gentamicin must be measured during therapy to ensure efficacy and prevent toxicity due to unduly high levels, especially in renal failure & the elderly. These measurements are usually carried out on two specimens of blood, the first taken one hour after and the second just before the next dose (trough concentration). One hour levels should be between 4- 10 mg/L and trough levels less than 2 mg/L. 3

Dosing of Gentamicin

The traditional dosing schedule of gentamicin is very effective in the eradication of many strains of bacteria but carries with it the serious adverse effects of ototoxicity & nephrotoxicity. But, because of its high efficacy and rare development of resistance, it has been important to understand the drug's pharmacokinetics so as to ensure the correct therapeutic levels without causing any toxic reactions. Substantial intra and inter- patient differences exist concerning the distribution volume and elimination rate constant of the drug for determining dose requirements. The pharmacokinetic dosing method has been recommended as the most important dosing method. The emergence of once daily aminoglycoside administration is attributed to several pharmacodynamic characteristics of the drug class, including: concentration

dependent killing, the post-antibiotic effect, a diminished propensity for adaptive resistance, and reduced toxicity. It was proved in a study that the once daily dosing regimen is preferred in critically ill patients. 4

Conclusion :

Gentamicin belongs to an important group of antimicrobial agents, Aminoglycosides, which is active primarily against the gram negative microorganisms. Due to their reduced rate of resistance development and susceptibility of most microorganisms that are resistant to all other common antimicrobial agents, the use of aminoglycosides is of prime importance in daily medical practice. But the serious adverse effects of ototoxicity and nephrotoxicity have reduced its use in practice. However, if the pharmacokinetic properties are critically evaluated and its dose regulated according to the patients' age, weight and renal function, the drug may be used without any adverse effect on the patient.

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