CHAPTER II

REVIEW OF LITERATURE

Gentamicin is a broad spectum aminoglycoside with high potency against both gram positive and negative bacteria especially gram negative rod bacilli. This agent in anaerobic condition is less effective so it has no effect to anaerobes such as Bacteriodes, Clostridium. Weinstein (1963) discovered this antibiotic and called it gentamicin. One year later Rosselot (1964) has stated that gentamicin is more broad spectrum than kanamicin and against Psuedomonas aeruginosa. Gentamicin is produced by fermentation of Micromonospora purpures compounding two molecules of garosamine binding to 2-deoxytreptamine.

Table 2.1 Presentation of microorganism which are sensitive by aminoglycosides.

Microorganism	Neomycin	Streptomycin	Kanamycin	Gentamicin	Tobramycin	Amikacin
Gram positive :						
Mycobacterium tuberculosis		✓[1]				✓
Staphylococcus species	✓			✓[2]	✓	✓[2]
Staphylococcus aureus			✓[2]	✓	✓	✓
Staphylococcus epidermidis			✓	✓	✓	✓
Streptococus species		✓[1]				
Streptococcus faecalis		✓[1]				
Gram negative :						
Acinetobacter species			✓	✓	✓	✓
Enterobacter species		✓		✓	✓	✓
Enterobacter aerogenes	✓	✓	✓			
Escherichia coli	✓	✓	✓	✓	✓	✓
Hemophilus influenzae		✓[1]	✓			
Hemophilus ducreyi		✓				
Klebsiella species	✓	✓	✓	✓	✓	✓
Morganella morganii			✓	✓	✓	✓
Neisseria gonorrhoeae		✓	✓			
Proteus species	✓	✓	✓[3]	✓[3]	✓[3]	✓[3]
Proteus mirabilis			✓	✓	✓	✓
Proteus vulgalis	✓		✓	✓	✓	✓
Providentia species				✓	✓	✓
Providentia rettgeri			✓	✓	✓	✓
Pseudomonas aeruginosa	✓[1]			✓[1]	✓	✓[1]
Salmonella species		✓	✓	✓	✓	✓
Serratia species			✓	✓	✓	✓
Yersinia pestis		✓	✓	✓	✓	✓

1 Usually used concomitantly with other antiinfective agents.
2 Penicillinase producing and nonpenicillinase inducing.
3 Indole-positive and indole-negative.

Mechanism of action

Gentamicin has many processes to be against bacterias as follows:

1. Gentamicin penetraets into bacterial cell wall by active transport and carrier using ubiquinone, cytochromes.
2. After penetration, gentamicin will inhibit protein synthesis by irrevesible ribosomal RNA binding resulted in misreading or misstranslation of amino acid.
3. Some protein produced by misreading is used as the structure. However, it is not the right structure and has pores on cell wall so gentamicin can easily penetrate through it. The easier gentamicin can penetrate, the more it inhibits. Finally, bacteria has a plenty of misreading protein.
4. Protein synthesized by ribosomal RNA working is inhibited completely if gentamicin concentration in bacterial cell become increased.
5. Gentamicin has inhibited bacterial growth by irrevisible machanism : penetration, ribosomal RNA binding, protein-synthesis inhibitation and induce cell function to defection (electron transfer process defection, RNA degradetion, abnormal DNA, DNA and RNA synthesis defection).

Pharmacokinetic

1. Absorption

Gentamicin is a positive polar antibiotic and well soluble in water but following oral administration, gentamicin is poorly absorbed from the gastrointestinal tract, with only 0.3% to 1.5% of an administrated dose appearing in the urine. Following systemic administration, it is administered by either intramuscular injection or intravenous infusion. It is generally well absorbed after intramuscular injection and it can be administered intravenously by bolus injection, by 30 to 60 minutes intermittent infusion, or by continuous intravenous infusion. Intermittent infusion of 30 to 60 minutes are thought to be safety and have additional therapeutic advantages. Continuous infusion have been suggested to improve the efficacy, especcially in neutropenia patients. Administration by continuous infusion would seem to lack therapeutic ratio, especially if the risk of tixicity is increased.

2. Distribution

Gentamicin distribute well into most body fluids including synovial, peritoneal, ascitic, and pleural fluids. This agent is not only distribute slowly in the bile, faces, prostate and amniotic fluid but also poorly in the central nervous system and the vitreous humor of the eye. Binding to serum proteins is less than 10%. Volume of distribution is about 0.2-0.5% litres per kilogram

In normal volunteers, the extracellular fluid compartment approximates 20% to 25% of body weight. This physiologic space is susceptible to changes that may occur during gram-negative sepsis (e.g., dehydration, congestive heart failure). Frequently, patients in initial phrase of gram-negative species are febrile, nausea, vomitting and dehydrated. As a result, the extracellular fluid compartment and drug volume are decreased in the dehydrated patients. In these

patients, the drug's distribution volume is markedly lower than 20% of body weight. Additionally, several subgroups of patients have been identified who are likely to have increases in drug distribution volume. These include patients who have congestive heart failure, patients with peritonitis, patients immediately postpartum, and patients receiving intravenous hyperalimentation. In addition, mewborn infants are known to have a larger extracellular fluid volume per unit of body weight. The drug's distribution volume in nonates is frequently in the range of 50 to 70% of body weight.

3 Excretion

Gentamicin is primarily eliminated unchanged by the kidney glomerular filtration. Active secretion may account for a small amount of drug eliminated by the kidney. Elimination by the kidney account for 98% of the dose administered and results in high urinary concentration after recommended dosages. Small amount of drug have been found in the bile and may represent an additional route of elimination.

The interpatient variation occur in patients who have a normal serum creatinine or a normal creatinine clearance. The magnitude of variation seems greater in patients being treated for gram-negative sepsis than in normal volunteers. This variation may also be greater in the initial phases of treatment, rather than later in the treatment course, when the patients' physiologic parameters have stabilized clinically. In volunteers who have normal renal function, the half-life of gentamicin was initially reported from 2.8 to 4 hours. Patients with impaired renal function have long-half life as 24 to 60 hours.

Factors related to gentamicin disposition

Several factors have been reported to alter the disposition of aminoglycoside antibiotics and thereby influence serum concentrations and dosage requirement. Additionally, specific patient conditions seem to influence the elimination of aminoglycosides and dosage requirements. Knowing these relationship, specific patients can better be selected who would benefit by more intensive serum concentration monitoring. The following variables and their relationship to aminoglycoside disposition warrant discussion.

- Renal function
- Age
- distribution volume
- Fever
- Hematocrit
- Ideal body weight
- Gender
- Obstetric patients
- Burn patients
- Pediatic patients
- Internal Medicine patients
- Ascites
- Geriatic patients
- Surgery / Critically III patients
- Cystic fibrosis
- Neonates
- Gynecologie patients

Side effect

Gentamicin is a narrow therapeutic ratio aminoglycoside so side effect or toxicity maysignificant occur.

1. Nephrotoxicity

Gentamicin nephrotoxicity is much more complex and difficult to separate from the complication secondary to underlying disease. Hypotention, shock, and renal failure may occur in the early phrases of gram-negative sepsis and result in acute tubular necrosis. In occational patients, these complications may occur during treatment and complicate the differential diagnosis for renal failure. Clinically and histologically, the changes in the kidney resulting from gentamicin toxicity, sepsis, or hypotention can not be differentiated, and the diagnosis then is based on clinical judgement. In some instances, the changes in renal function may initially be due to underlying disease which may then decrease gentamicin elimination, increase serum concentration of gentamicin, and cause furthern damage to the nephron. Measuring serum concentration and adjusting the dosage regiment of gentamicin may prevent further insult to the kidney after the septic changes have occured.

Gentamicin for long term treatment, Nephrotoxicity may occur specially at proximal renal tubule because gentamicin have been excreted completely by renal glomerular filtration in unchange form. Some of them have been absorbed by pinocytosis to proximal renal tubular cell at proximal loop and collected in liposome that proximal tubular cell have eliminated in from of phospholipid multicellular myeloid. Because of prolong gentamicin collection in renal cortex that concentration is more than 5 to 50 times from serum concentration resulting to all damaged, (due to gentamicin inhibited cell wall enzymes such as Mitochondria dysfunction, glomerular filtration rate decreased, renal tubular cell damaged and tubular cell necrosis.

Degree of toxicity depend on serum gentamicin concentration, dose, duration of treatment and time of gentamicin collecting in renal cortex. Continuous infusion for prolong treatment may cause more nephrotoxicity than intermittant infusion. The trough concentration has indicated drug collecting in renal cortex. The higher trough concentration over 2 ug/ml has been the high risk of nephrotoxicity and ototoxicity because of low drug excretion and high drug collecting in renal tubule resulting to high serum gentamicin concentration.

Nephrotoxicity secondary to use of gentamicin classically occurs at least five days after the initiation of treatment . Typical findings generally include decreased glomerular filtration rate, increased serum creatinine, increased blood urea nitrogen, and impaired urinary concentrating ability ; these factors result in non-oliguric renal failure. Additionally, proteinuria, aminoaciduria, glycosuria, and electrolyte disturbances also occur. The proximal tubule is thought to be the primary site of gentamicin nephrotoxicity. Markers of renal tubular function such as β_2-microglobulins, urinary casts, and urinary enzymes have been suggested as a means of detecting early renal damage and preventing severe damage to the kidney. These markers are not specific for gentamicin induced nephrotoxicity and thus have not been widely used. Patients who have a rise in serum creatinine should be evaluated for continued need of gentamicin therapy. In those patients requiring further therapy, serum concentrations should be monitored to prevent further accumulation and further renal damage. In most patients, the changes in renal function are reversible, provided that the infectious entity is adequately treated and further drug accumulation does not occur. During the early phases of recovery, high output failure generally occurs, and glomerular filtration generally improves slowly thereafter. The clearance of gentamicin may not improve in parallel with improvements in filtration, and, many times, improvement in function as estimated by aminoglycoside clearance is substantially delayed. Dosage requirements of gentamicin are greatly reduced during this period of time, and serum monitoring is imperative if safe serum concentrations are to be maintained. Several factors have been associated with a higher risk of nephrotoxicity.

These include increasing age, compromised renal function, volume depletion, documented infection, total dose, duration of treatment, prior exposure to gentamicin, peak concentration, trough concentration, and concurrent exposure to nephrotoxic drugs (e.g., cephalosporins). Several of these risk factors may result in increased concentration of gentamicin, and thereby the risk factor is more directly associated with elevated serum concentrations. For example, older patients are known to have decreased elimination of gentamicin. if older patients recieve the standard dose, higher serum concentrations would occur and might predispose these patients to a higher risk of nephrotoxicity. Other factors may have a similar association with decreased elimination or increased serum concentrations. Controlling concentrations serum more directly may decrease the risk of toxicity associated wkth these specific factors.

Table 2.2 Summary of Risk Factors Associated With Toxicity

Ototoxicity	Nephrotoxicity
Age	Age
Impaired renal function	Renal insufficiency
Dehydration	Elevated trough concentrations
Elevated trough concentrations	Elevated peak concentrations
Elevated peak concentrations	Total daily dose
Total daily dose	Cumulative dose
Cumulative dose	Concurrent nephrotoxic drugs
Concurrent ototoxic drugs	Prior aminoglycoside exposure
Prior aminoglycoside exposure	Hypovolemia
Dialysis	Gender
Duration of treatment	Duration of treatment
	Sepsis

2. Ototoxicity

One problem with all aminoglycosides is the possibility of eighth cranial nerve toxicity which includes auditory and vestibular dysfunction. It can occur during treatment or up to four to six weeks afier termination of treatment. The symptoms of early cochlear toxicity include a sensation of fullness and tinnitus. Gentamicin are thought to alter the sodium-potassium pump , there by causing a change in the electrical potential and intracellular osmotic pressure within the endolymph. Early changes primarily affect the outer hair cells of the organ of Corti and initially affect higher frequencies such as 4000, 6000, or 8000 Hz. The early stage of toxicity generally does not affect frequencies utilized in conversational hearing. The toxic changes are generally reversible at this early stage. With more severe toxicity, the outer hair cells of the organ of Corti are destroyed , and the hair cells of the apex become damaged. Hearing impairment then occurs at lower frequencies, and conversational hearing is compromised. These auditory deficits are usually bilateral, but can be unilateral. At this later stage, the deficit is generally permanent or only partially reversible. Vestibular dysfunction generally parallels cochlear damage and is usually manifested by vertigo, nausea , dizziness, and nystagmus. The vestibular damage is usually permanent; however, the patient can generally overcome the deficit by other compensatory mechanisms (e.g., vision). Several factors have been associated with a higher incidence of ototoxicity. These include duration of treatment, cumulative dose, average daily dose, peak serum concentration, trough serum concentration, concurrent diuretics such as furosemide or ethacrynic acid, underlying disease states, and previous exposure to aminoglycoside therapy. Elderly patients apparently have a higher risk of toxicity than do younger patients. Patients with compromised renal function, particularly those requiring hemodialysis, may have an increased risk of toxicity. One study, however, demonstrated a similar incidence of toxicity in patients with normal and abnormal renal function when the serum concentration of gentamicin was maintained in the therapeutic range.

3. Neuromuscular blockade

Gentamicin associated neuromuscular blockade was first thought to be rare, however, this potentially serious side-effect may occur with a greater frequency than thought initially. This reaction is more likely to occur when gentamicin is administered intravenously and concurrently with other neuromuscular blocking agents or anesthetic agents such as ether, tubocurarine, succinylcholine, decamethonium, or gallamine. Additionally, patients who are hypocalcemic of who have existing neuromuscular diseases, such as myasthenia gravis of botulism, are more susceptible to neuromuscular blockade. The mechanism of gentamicin induced neuromuscular blockade involves interference with calcium and with the immediate release of acetylcholine presynaptically. The onset is characterized by respiratory failure and/or muscle weakness. In mild cases, discontinuation of gentamicin usually suffices to reverse toxicity; however, in more severe cases, therapeutic intervention may be required with administration of calcium gluconate or neostigmine.

4. Others

Other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, blood dyscrasias, angioedema, arthralgia, anemia, hypotension, anaphylactic shock, hypomagnesemia, diarrhea, thombocytopenia, neutropenia, agranulocytosis and aplastic anemia.