CHAPTER II

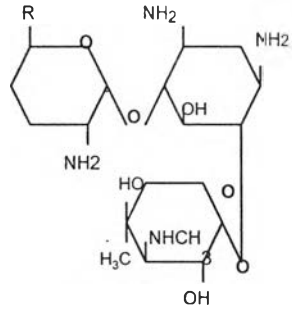
REVIEW OF LITERATURE

I. REVIEW OF GENTAMICIN SULFATE

A. Physical and chemical properties

Gentamicin is an aminoglycoside isolated form Micromonospora purpurea.[5,34] The commercially available drug is mixture of the sulfate salts of gentamicin C_1, C_2, and C_{1A} : all 3 components appear to have similar antimicrobial activity.[5]

FIGURE 1 The structure of gentamicin sulfate.



Gentamicin	R	Molecular weight
C1A	CH_2NH_2	$C_{21}H_{43}N_5O_7$ (M.W. = 477.6)
C2	$CH(CH_3)NH_3$	$C_{20}H_{41}N_5O_7$ (M.W. = 468.6)
C1	$CH(CH_3)NHCH_3$	$C_{19}H_{39}N_5O_7$ (M.W. = 449'5)

Gentamicin C_{1A} is O–3deoxy–4–C–methyl–3–(methylamino)– β–L arabinopyronosyl – (1 – 6) – O – [2,6 – diamino – 2,3,4,6 – tetradeoxy - α - D – erythro – hexopyranosyl – (1 – 4) – 2 – deoxy – D – streptamine.[5, 35-36]

B. Description

White to buff powder: odorless; stable in light, air, and heat; melts with decomposition between 220 and 240° C [36]

C. Solubility

Soluble in water; insoluble in alcohol, acetone, chloroform, and ether. [36,38]

D. Stability

Gentamicin sulfate injection should generally be stored at a temperature less than 40°C, preferably between 15 – 30°C, unless otherwise specified by the manufacturer; freezing should be avoided. Gentamicin sulfate is stable for 24 hours at room temperature in most IV infusion fluids including 0.9% sodium chloride or 5% dextrose injection. The manufacturers state that gentamicin sulfate injection for IV administration should not be mixed with other drugs.[5]

Gentamicin sulfate intrathecal and piggyback contain no preservatives. The manufacturer recommends that they should be used immediately after opening and that any unused portions should be discarded.[37]

There was an average 16 % potency loss of gentamicin sulfate on storage at 4 or 25°C in plastic disposable syringes for 30 days, and a brown precipitate formed in several. Storage in glass disposable syringes for 30 days produces an average 7% potency loss, which was considered acceptable, but storage for longer resulted in precipitated formation in some cases and was not recommended.[38]

E. Antibacterial spectrum

Gentamicin is one of aminoglycoside antibiotic which is active against strains of Gram – negative bacteria.[38] It has broad spectrum antibacterial activity.[36]

Table 2.1 Microorganisms which are sensitive to gentamicin.[39]

Organisms	Susceptible to gentamicin
Gram – positive	
Staphylococcus aureus	1
Streptococcus faecalis	2
Staphylococcus species	3
Gram – negative	
Citrobacter species	1
Enterobacter species	1
Escherichia coli	1
Klebsiella species	1
Proteus species	4
Providencia species	1
Pseudomonas species	2
Salmonella species	1
Serratia species	1
Shigella species	1
Yersinia (Pasteurella) pestis	1

1 = Generally susceptible

2 = Usually used concomitantly with other anti – infectives

3 = Penicillinase – producing and nonpenicillase – producing

4 = Indole – positive and indole - negative

F. Mechanism of action

The aminoglycoside antibiotics are rapidly bactericidal. Bacterial killing is concentration dependent: the higher the concentration, the greater the rate at which bacteria are killed. A postantibiotic effect, that is, residual bactericidal activity persisting after the serum concentration has fallen below the minimum inhibitory concentration, also is characteristic of aminoglycoside antibiotics, and the duration of this effect is concentration dependent. These properties probably account for the efficacy of once daily dosing regimen of aminoglycosides despite long periods during which antibiotic is not present. The effect with aminoglycosides varies with specific bacterial pathogens and might be related to irreversible binding to bacterial ribosomal subunits with subsequent disruption of protein synthesis. The PAE associated with aminoglycosides may represent the time needed to synthesize new ribosomes. Aminoglycosides typically exhibit a PAE of 2 hours or less with gram – positive organisms and a 2 – 4 hours PAE with gram – negative bacilli. Combining other antibiotics with aminoglycosides might extend the PAE for some organisms[40,41]

Although much is known about their capacity to inhibit protein synthesis and decrease the fidelity of translation of mRNA at the ribosme (not mamalian) these effects do not provide an obvious explanation for the rapidly lethal effect of aminoglycosides on bacteria.[34,40]

Aminoglycosides diffuse through aqueous channels formed by porin proteins in the outer membrane of gram negative bateria and thereby enter the periplasmic space. Subsequent transport of aminoglycosides across the cytoplasmic (inner) membrane is dependent on electron transport, in part because of a requirement for a membrane potential (interior negative) to drive permeation of these antibiotics. This phase of transport has been termed energy dependent phase I. It is rate limiting and can be blocked or inhibited by divalent cations (e.g. Ca^{2+} and Mg^{2+}), hyperosmolarity, a reduction in P^{H}, and anaerobiasis. The last two of these conditions impair the ability

of the bacteria to maintain the driving force necessary for transport (membrane potential).

Following transport across the cytoplasmic membrane, the aminoglycosides bind to polysomes and interfere with protein synthesis by causing misreading and premature termination of translation of mRNA. The aberrant proteins produced may be inserted into the cell membrane, leading to altered permeability and further stimulation of aminoglycoside transport . This phase of aminoglycoside transport, termed energy dependent phase II (EDP_2) is poorly understood; however, it has been suggested that EDP_2 is in some way linked with disruption of the structure of the cytoplasmic membrane, perhaps by the aberrant proteins. This concept is consistent with the observed progression of the leakage of small ions, followed by larger molecules and, eventually, by proteins from the bacterial cell prior to aminoglycosides induced death. This progressive disruption of the cell envelope, as well as other vital cell processes, may help to explain the lethal action of aminoglycosides.

The primary intracellular site of action of the aminoglycosides is the 30s ribosomal subunit, which consists of 21 proteins and a single 165 molecule of RNA. Aminoglycosides also bind to 30s ribosomal subunit; however, they also appear to bind to several sites on the 50s ribosomal subunit as well.

Aminoglycosides disrupt the normal cycle of ribosomal function by interfering, at least in part, with the initiation of protein synthesis, leading to the accumulation of abnormal initiation complexes. Another effect of the aminoglycosides is their capacity to induce misreading of the mRNA template, and incorrect amino acids are incorporated into the growing polypeptide chains.[40]

G. Resistance

Streptococci and *enterococci* are relatively resistant to gentamicin owing to failure of the drug to penetrate into the cell. However, gentamicin in combination with vancomycin or a penicillin produces a potent bactericidal effect, which in part is due to enhanced uptake of drug that occurs with inhibition of cell wall synthesis. Resistance to gentamicin rapidly emerges in *staphylococci* due to selection of permeability mutants. Ribosomal resistance is rare. Among gram-negative bacteria, resistances is most commonly due to plasmid-encoded aminoglycoside modifying enzymes. Gram negative bacteria that are gentamicin resistant usually will be susceptible to amikacin, which is much more resistant to modifying enzyme activity. The enterococcal enzyme that modifies gentamicin is a bifunctional enzyme that also modifies amikacin, netilmicin, and tobramycin, but not streptomycin; the latter is modified by a different enzyme. This is why some gentamicin – resistant *enterococci* are susceptible to streptomycin.[34]

H. Pharmacokinetic

1. Absorption

a. Oral

Gentamicin is poorly absorbed from the GI tract. The drug is well absorbed following parenteral administration.[3,5,34,38] However, oral gentamicin has been used to prevent necrotizing enterocolitis (NEC) in very low birth weight infant.[3]

b. Intramuscular

Intramuscular administration of gentamicin is cited as a possible route of delivery, with peak plasma concentrations of about 4 mg/l have been obtained in patients with normal renal function 30 to 60 minutes after injection of a dose equivalent to 1 mg of gentamicin per kg by body–weight.[3,38] For intramuscular absorption to occur, however, there must be adequate blood flow to and from the injection site. In compromised neonates – those experiencing poor perfusion due to cardiac, respiratory, and gastrointestinal disease states; vasoconstriction secondary to hypothermia; as well as vasomotor instability; the degree of absorption from an intramuscular injection is unpredictable. Skeletal muscle mass and subcutaneous fat are also lower in the neonate, limiting the number of available injection sites and the amount of solution that can be administered at each injection sites.[3]

c. Intravenous

For the ill neonate, the intravenous route of delivery is preferred because the gentamicin immediately enters the systemic circulation. Gentamicin may be mixed with D5W, D10W, NS and TPN and infused over 30 minutes.[3]

2. Distribution

Following parenteral administration gentamicin and other aminoglycosides, distribute mainly into extracellular fluids. However, there is little distribute into the cerebrospinal fluid and even when the meninges are inflamed effective concentrations may not be achieved; distribution into the eye is also poor. Aminoglycosides distribute readily into the perilymph of the inner ear. Gentaminicin crosses the placenta but only small amounts distribute into breast milk, bile, sputum, saliva and tears.[38,42] Binding to plasma protein is low (< 30%). In average, volume of distribution for

gentamicin is about 0.2 – 0.3 l/kg in adults, 0.3 ± 0.1 l/kg in adolescents, 0.35 ± 0.15 l /kg in children, 0.4 ± 0.1 l/kg in infants and 0.45 ± 0.1 l /kg in neonate.[42] Peak serum concentrations may be changed from usual in patients whose extracellular fluid volume is change, which may occur during sepsis (dehydration), congestive heart failure, fever, liver disease, edema or ascites, burn, obese and malnutrition.[43 - 45]

In the neonate, drug distribution is largely a function of body composition. The full - term neonate' s body weight at birth is composed of approximately 75 percent water, most of which is extracellular. As gestational age decreases, both total body water and extracellular fluid volume increases. Water soluble drugs, like gentamicin, are largely distributed in the extracellular fluid. Neonates are therefore described as having a larger volume of distribution for water soluble drugs. With gentamicin, differences in body composition result in the neonate 's having a larger milligram per kilogram dosage requirement than the adult.[3,46]

The large volume of distribution for gentamicin seen in neonates has led to research regarding the need for a loading does to achieve therapeutic serum concentrations. The delay in attaining therapeutic peak levels in the first 24 hours of treatment has been correlated with increased mortality. The minimum inhibitory concentration that inhibits organism growth. For most gram negative bacteria, that concentration is 1 – 4 mg/l, depending on the organism. Loading doses of 3.5 – 5 mg/kg have been recommended and shown to produce a peak of 5 µg /ml 60 to 90 minutes post infusion. These initial loading doses are then followed by standard dosage regimens. Loading doses have not been shown to affect the eventual steady state achieved with maintenance dosages or been correlated with an increased risk of toxicity.[3 – 46]

3. Elimination

Gentamicin and other aminoglycosides do not appear to be metabolized and are excreted virtually unchanged in the urine by glomerular filtration.[38] In adults with normal renal function, 50 – 93% of a single IM does of gentamicin is excreted within 24 hours. Peak urine concentrations of gentamicin may range from 113 – 423 mg/l 1 hour after a single IM dose of 1 mg / kg in adults with normal renal function. Complete recovery of the dose in urine requires approximately 10 – 20 days in patients with normal renal function.[5]

The plasma elimination half life of gentamicin is usually 2 – 3 hours in adults with normal renal impairment. The plasma elimination half life of gentamicin averages 3 – 11.5 hours in neonates < 1 week of age, 3 – 6 hours in neonates 1 week to 1 month of age, 4 ± 1 hours in infants, 2 ± 1 hours in children, and 1.5 ± 1 hours in adolescents.[5,42]

The half life of gentamicin in the full – term neonate may exceed 5 to 6 hours due to decreased glomerular filtration.[47] Nephrogenesis is completed by 34 to 36 weeks gestation. Neonates born prior to this time will have a decreased glomerular filtration rate until this age postconceptually. Because of the decreased glomerular filtration rate, especially in the premature neonate, the elimination half life of gentamicin is prolonged. A high millgram per kilogram dose is necessary because of the large volume of distribution for gentamicin; however, the dosing interval for preterm infant needs to be lengthened to promote clearance of the drug.[3,46]

The use of serum creatinine levels to approximate serum gentamicin half life has been identified as an effective guide for dosing.[9–3] The creatinine clearance level is the best estimate of kidney function, but it is impractical to measure this level in the neonate. Serum creatinine has been shown to correlate roughly with aminoglycoside gentamicin levels.[3] Reimche and colleagues demonstrated in neonates that gentamicin

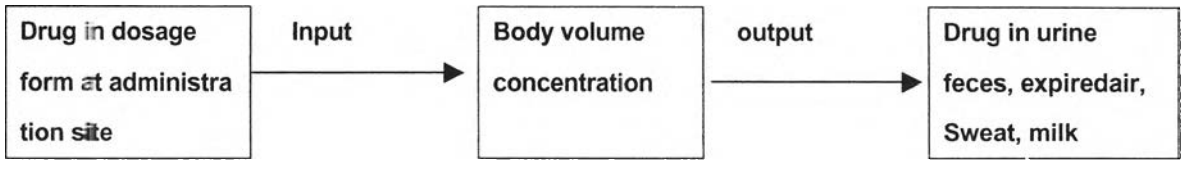
dosing based on serum creatinine levels produces reasonable therapeutic serum gentamicin concentrations, without evidence of toxicity. The benefits of measuring serum creatinine as opposed to actual gentamicin peak and trough levels are that less blood is required and fewer chances exist for the errors in timing, handling, and assaying that may occur when drawing drug levels.[3,48] The disadvantage of using serum creatinine to evaluate gentamicin dosing is that some studies have shown plasma creatinine to vary widely in the first 30 days of life, with higher values noted especially during the first 10 days of life.[3]

4. Pharmacokinetic model

A one–compartment model is generally assumed for gentamicin pharmacokinetic calculations. The initial distribution phase following a gentamicin intravenous infusion is not a factor when the one – compartment model is utilized for gentamicin pharmacokinitic calculations. For this reason, reported values for plasma samples obtained near the conclusion of an intravenous infusion may be higher than expected. The errors encountered when using this model can be minimized if plasma drug concentrations are obtained at times that avoid the first and third distribution phases and at 24 hours after therapy has been initiated.[15]

In one–compartment model, the drug entering the body (input) distributes (equilibrates) instantly between the blood and or their body fluids or tissues.[49]

Figure 2 concept of one – compartment model



I. Gentamicin blood sampling and assay considerations[19]

Peak concentrations should be drawn after distribution is complete (30 to 60 minutes after the completion of the intravenous infusion). In some patient, the distribution time may be prolonged and sampling of peak concentrations should be delayed to make sure distribution has been completed e.g. in patients with ascites from cirrhosis, peak concentrations should be obtained at least 2 hours after completion of a infusion (60 minutes). Patient receiving intramuscular administration can have peak concentrations obtained from 1 to 1 ½ hours after the does is injected. In patients with diabetes, spinal cord injury, and septic shock, the peak levels may be delayed when the aminoglycosides are given intramuscularly.

A trough concentration is obtained within 30 minutes prior to the next dose. Blood samples should be obtained in the arm opposite the one in which the drug is being infused. This maneuver avoids the possible false elevation of a serum concentration due to back flow of antibiotic into the vein being sampled.

Peak and trough concentrations are best obtained at steady state that usually achieved after the medication has been administered for about five half lives. The serum creatinine should be obtained every 2 to 3 days in the stable patient and every other day in the patient with risk factors for toxicity or changing clinical condition.

To be able to interpret the serum concentration data appropriately, the exact sampling time, infusion time, and time of last does must be available.[19]

J. Indication[39]

1. Treatment of serious infections caused by susceptible strains of *Pseudomonas aeruginosa, Proteus sp* (indole – positive and indole –

negative), *Escherichia coli, Klebsiella sp, Enterobacter sp*, *Serratia sp, Citrobacter sp*, and *Staphylococcus sp* (coagulase positive and coagulase – negative).

2. Effective in bacterial neonatal sepsis; bacterial septicemia; serious bacterial infection of the CNS (meningitis), urinary tract, respiratory tract, GI tract (including peritonitis), skin ,bone and soft tissue (including burns).

3. Not indicated in uncomplicated initial episodes of urinary tract infections, unless causative organisms are susceptible to these antibiotics with less potential for toxicity. Perform bacterial cultures.

4. Gram – negative infection: consider as initial therapy in suspected or confirmed gram–negative infection; therapy may be started before obtaining results of susceptibility testing, but continue therapy based on susceptibility test, results and infection severity.

5. Unknown causative organisms: in serious infections, administer gentamicin as initial therapy in conjunction with a penicillin or cephalosporin before obtaining results of susceptibility test. Following identification of the organism and its susceptibility continue appropriate antibiotic therapy.

6. Combination therapy: effective in combination with carbenicillin for the treatment of life–threatening infections caused by *Pseudomonas aeruginosa*. Also effective when combined with a penicillin for treatment of endocarditis caused by *group D streptococci*. In the neonate with suspected bacterial sepsis or *staphylococcal* pneumonia, penicillin is usually indicated concomitantly with gentamicin.

7. Staphylococcal infection: while not the antibiotic of first choice, considers gentamicin when penicillins or other less toxic drugs are contraindicated, when bacterial susceptibility tests and clinical judgment indicate its use and in mixed infections caused by susceptible strains of *staphylccocci*, and gram – negative organisms.

8. Intrathecal administration is indicated as adjunctive therapy to systemic gentamicin sulfate in the treatment of serious CNS infections (meningitis , ventriculitis) caused by susceptible *Pseudomonas sp.* Perform bacteriologic test to determine that the causative organisms are susceptible to gentamicin.

9. Unlabeled uses: an alternative regimen for pelvic inflammatory disease is gentamicin 2 mg/kg IV followed by 1.5 mg/kg 3 times daily (normal renal function) plus clindamycin 600 mg IV 4 times daily. Continue for at least 4 days and at lest 48 hours after patient improves; then continue clindamycin 450 mg orally 4 times daily for 10 to 14 days total therapy.[39]

K. Therapeutic efficacy

Gentamicin is among the most frequently selected agents which therapeutic drug monitoring required, because of the narrow therapeutic range of the aminoglycoside antibiotics and reports of large intersubject variability in half–life and volume of distribution. Therapeutic drug monitoring has been recommended in an attempt to provide maximal potential benefit with minimal risk of toxicity.[8 – 12]

When gentamicin is given 2 or 3 times per day, desired therapeutic peak are between 4 – 12 mg/kg.[4 - 5,14,16 -18 38 - 40] Peak serum concentration higher than 4 mg/L are reported to elect better response in patient with serious gram – negative bacillary infection.[4, 14, 16] Trough concentration of the drug should not exceed 1–2 mg/L. Some evidence suggests that an increased risk of renal toxicity may be associated with

trough concentration greater than 2 mg/L.[5, 15, 19] Ototoxicity has been associated with trough plasma concentration of gentamicin exceeding 4 mg/L for more than ten day.[15] When a once daily dose regimen is used, Peak level are not necessary.[19,34] Trough concentration of gentamicin should not exceed 2 mg/L Trough concentration of gentaminic is frequently recommended below 1 mg/L.[20,34]

L. Dosage

Gentamicin may be given IM or IV. For patient with serious infection and normal renal function, given 3 mg /kg/ day in equal dose every 8 hours. For patients with life – threatening infections, administer up to 5 mg / kg / day in 3 or 4 equal doses Reduce dosage to 3 mg/ kg / day as soon as clinically indicated.[39] In children, give 2 – 2.5 mg / kg every 8 hours, Infants give 2.5 mg / kg every 3 hours.[38 – 39] In preterm neonate, weight less than 1,000 g, give 3.5 mg/kg/day. In preterm neonate, weight less than 1,200 g that have 0 – 4 weeks of age, give 2.5 mg/kg/dose every 18–24 hours. In neonate (postnatal age $\leq$ 7 days) weight 1,200 – 2,000 g, give 2.5 mg/kg dose every 12 – 18 hours, weight more than 2,000 g, give 2.5 mg/kg /dose every 12 hours. In neonnate (postnatal age> 7 days) weight 1,200 – 2,000 g, give 2.5 mg/kg dose every 8 – 12 hours and weight more than 2,000 g give 2.5 g/kg/dose every 8 hours.[38 – 39,42]

The course of a treatment should generally be limited to 7 to 10 days. In difficult and complicated infection, a longer course of therapy may be necessary. In such cases, monitor renal, auditory and vestibular functions since toxicity is more apt to occur with treatment extended beyond 10 days. Reduces dosage if clinically indicated.[38–39] Alternatively, many clinicians recommend that gentamicin dosage be determined using appropriate pharmacokinetic methods for calculating dosage requirement and patient – specific pharmacokinetic methods for calculating dosage requirements and patient – specific pharmacokinetic parameter (e.g. elimination rate

constant, volume of distribution) derived from serum concentration – time data: in determining dosage, the susceptibility of the causative organism, severity of infection, and the patient's immune and clinical status also must be considered.[5]

Single daily dose

Rapidly developing antibiotic resistance has created a need for better use of currently available agents and the development of newer, more effective agents and therapeutic approaches. One of these newer approaches is the administration of aminoglycosides in large single daily doses.[29,41] The concept of a once daily dosing (ODD) of aminoglycoside or single daily dose (SDD) has evolved over the past 10 years.[23] ODD usually refers to a single fixed daily aminoglycoside dose which is administered every 24 hours. The promoted dose is typically equivalent to the sum of doses traditionally administered over a 24 hours period, using 3 to 7 mg/ kg of gentamicin, tobramycin or netilmicin, and 10 to 20 mg/kg of amikacin.[23,27]

The theoretical benefits of ODD scheme are based on several pharmacodynamic properties of aminoglycosides, in term of both efficacy and toxicity. Aminoglycosides have concentration–dependent killing, ie, increasing concentration kill an increasing proportion of bacteria and at a more rapid rate.[34,41] In vitro experiments, animal models ,and human data have supported the concept that increasing the peak serum concentration or maximizing the concentration in the plasma divided by the minimum inhibitory concentration(MIC), (The C_{pmax}–to– MIC ratio) results in a more rapid kill rate and in a greater percentage of bacteria killed. C_{pmax} to – MIC ratio of 8 – 20 have been recommended to achieve optimal aminoglycoside activity.[50-52]

Barclay et al[53] reported that higher initial gentamicin concentration not only produced greater bactericidal activity resulted in a more prolonged and marked adaptive resistance. In addition, aminoglycosides have a significant postantibiotic effect (PAE). PAE is defined as the time when serum concentrations are below the

MIC for a particular pathogen. One large dose of an aminoglycoside, as with once daily dosing, produces a much higher serum concentrations which are associated with a longer PAE.[23,41]

Toxicity of once daily dosing of aminoglycoside was studied in both animal models and clinical studies. In animal models of aminoglycoside ototoxicity and nephrotoxicity, once daily dose regimens are less toxic than multiple – dose regimens for the same total dose. Numerous clinical studies demonstrate that a once daily dose of aminoglycoside is just as effective and no more (and often less) toxic than multiple smaller does.[5, 23, 34,38]

Once–daily dosing schemes do appear to represent potential cost saving alternatives to multiple daily dosing schemes.[23] Once–daily also has several practical advantages. Once–daily administration offers less frequent dosing, decreased nursing time, and less use of infusion devices compared with the standard every 8 – 12 hour dosing.[28,34]

There is no need to obtain serum concentrations unless the intention is to administer aminoglycoside for more than 4 or 5 days. The most common problem with aminoglycoside usage – ie. subtherapeutic serum concentrations due to underdosing drug because of a legitimate fear of toxicity is eliminated. Aminoglycoside toxicity is both time and concentration dependents. Toxicity is when a threshold concentration is achieved and correlate with the time above this threshold. This threshold is imprecisely defined, but a trough concentration above 2 mg / l is predictive of toxicity. At clinically relevant does, the time above this threshold will be greater with multiple smaller dose of drug than with a single large dose.[34]

Wide variation in aminoglycoside concentration can be expected if a fixed ODD scheme is employed.[23] Use of ODD does not eliminate responsibility for careful monitoring and dosage adjustment to minimize toxicity. Selection of the appropriate dose

or dosing interval is particularly critical if renal insufficiency is present.[23, 34, 41] The use of ODD in pregnant, pediatric, geriatric, and critically ill patients, and in any patient with moderate – to – severe renal dysfunction, neutropenia, burns, liver disease, or endocarditis, represents areas in which relevant trials are needed. Until then, the use ODD should be undertaken with caution.[41]

M. Adverse reaction and toxicity

The most common toxicities of gentamicin and aminoglycosides in general are nephrotoxicity and ototoxicity.[3]

1. Nephrotoxicity

Approximately 5 % to 25% of patients who receive gentamicin for longer than 3 – 5 days will develop mild renal impairment.[34,40 – 41] Toxicity correlates with the total amount of drug administered. Consequently toxicity is more likely to be encountered with longer course of therapy.[40] Nephrotoxicity is associated with a reduction in glomerular filtration rate impaired concentration ability, increased serum creatinine and increased urea nitrogen. High trough levels, greater than 2 mg/l is usually associate with toxicity[3,5,41,54]

The nephrotoxicity of gentamicin is reported to be largely due to the gentamicin C_2 component.[38] The aminoglycoside antibiotics are intrinsically nephrotoxic . These antibiotics are highly polar drugs which cross biological membranes poorly, but they are filtered by the glomerulus and bind to the brush border of the proximal convoluted tubules at the same negatively changed binding sites that attract basic amino acids.[29,30] The nephrotoxic potential varies among individual aminoglycosides. The relative toxicity correlates with the concentration of drug found in the renal cortex in experimental animal .[40] The number of amino groups available for binding to these receptors correlates somewhat with their nephrotoxic potential. Neomycin (most

nephrotoxic) has six ; gentamicin, tobramycin, amikacin and netilmicin have five; and streptomycin (least nephrotoxic) has two free amino groups.[19] Neomycin, which concentration to the gratest degree , is highly nephrotoxic in human beings and should not be administered systemically. Streptomycin does not concentrate in the renal cortex and is the least nephrotoxic.[40] The relative nephrotoxicities of the other aminoglycosides in humans have not been definitely established; however, tobramycin appears to be less nephrotoxic than gentamicin because of its lower accumulation in the kidney versus gentamicin.[5,19,40]

The mechanism of nephrotoxicity is possibly related to the inhibition of intracellular phospholipases in lysosomes of tubular cell in the proximal tubule.[41] Aminoglycoside are highly polar drug which cross biological membranes poorly or not at all, but they are filtered by the glomerulus, after entering the luminal fluid of proximal renal tubule a small protion of the total filtered drug is reabsorbed and stored in the proximal tubular cell.[30] Aminoglycosides bind to phosphatidylinositol within the renal tubular cell membrane in the renal cortex and undergo internalization by pinocytosis.[41,55] Binding to renal tubular cell membranes also results in the increased of brush border enzymes, as well as calcium and magenesium.[41] The lysosomes have been identified as the first organelles to show alterations during aminoglycoside treatment. Aminoglycosides tend to accumulate extensively inside the lysosomes, because pinocytosis is a continuing phenomenon.[56]

Aminoglycosides inhibit lysosomal phospholipases and sphingomyelinase in the lysosomes of proximal tubular cells, resulting in lysosomal phospholipidosis, with a non – specific accumulation of polar phospholipids in myeloid bodies. When a threshold in cortical drug concentration is reached , the lysosomal phospholipidosis progresses and the overloaded lysosomes continue to swell, resulting in the loss of integrity of the restricting membrane of lysosomes and release of large amounts of aminoglycosides , lysosomal enzymes and phospholipids into the cytosol. The extralysosomal aminoglycosides can gain access to other organelles, disturbing

their functional integrity which may lead to cell death.[30] The net result is the necrosis of the proximal tubular cell, leading to the reduction of glomerular filtration and a fall in creatinine clearance levels.[41]

The initial manifestation of aminoglycoside nephrotoxicity is enzymuria. These enzymes may arise from the loss of brush border membranes of the proximal tubule. Urinary excretion of lysosomal enzymes can also be seen. As damage continues, tubular resorptive function is affected and tubular proteinuria (ie, β2 – microglobinuria), aminoaciduria , glycosuria, and magnesium and potassium wasting are noted. Urine sodium concentrations also increase. Polyuria and nephrogenic diabetes insipidus develop in early nephrotoxicity. In most cases, the renal insufficiency is nonoliguric and reversible following discontinuance of the drug (weeks to months may pass before return of baseline function) [19] since the proximal tubular cells have the capacity to generate; however , death due to uremia has occurred rarely.[3,5,34,40 – 41] The severe acute tubular necrosis may occur rarely, the most common significant finding is a mild rise in plasma creatinine (0.5 – 2.0 mg/dl; 40 to 175 μM above baseline); hypokalemia, hypocalcemia and hypophosphatemia are seen very infrequently.[19,40 – 41] Oliguric renal failure is less common and can be acute or follow the nonoliguric variety.[19]

Laboratory test for urinary enzymes, urinary β_2 – microglobulin, and urinary cast excretion have been developed to detect proximal tubule damage prior to elevation of serum creatinine in patients receiving aminoglycoside. These tests, however, are not specific enough to always differentiate drug – versus disease induced kidney damage and remain research tool.[19] Risk factors for aminoglycoside nephrotoxicity are listed in table 2.2 [19,30,40 – 41]

Table 2.2 Potential risk factors for aminoglycoside nephrotoxicity

Drug – related	Patient related
- Dose	- Age
duration	- Sex (male gender)
dosage regimen	
- Prior aminoglycoside treatment	- Preexisting kidney disease
- Choice of drug	- Presence of liver disease
- Prolonged high trough levels	- Volume depletion
- Associated drugs	- Shock
diuretics	- Other causes
cyclosporin	
cisplatin	
amphotericin	
vancomycin	
methoxyflurane	
NSAID	
ACEI	

Risk factors for nephrotoxicity include advanced age,male gender, preexisting renal impairment, volume depletion, prior aminoglycoside treatment, presence of liver disease, shock, choice of drug, prolonged high trough levels, and associated drug. [19,30,40-47,57-58]

The risk of toxicity increases with prolonged therapy and in patients receiving repeated course separated by a few days or weeks, since it determines the extent of drug uptake.[19,41,59] Dosage regimen is determines the extent of cortical aminoglycoside concentrations. Nephrotoxicity is more severe when total daily dose is divided or given by continuous infusion than single bolus in some experimental.[22,41,57,60-61]

Controversy exists over the importance of trough concentration as risk factors for nephrotoxicity. Dahlgren et al noted that 36% of patients with nephrotoxic effects had trough gentamicin concentration greater than 2 mg/l. No patient with trough concentration below 2 mg/l had an increase in serum creatinine. In contrast, 64% of patients with trough concentrations greater than 2 mg/ l showed no deterioration of kidney function. In one study, a trough gentamicin concentration of 4 mg/ l or greater was associated with nephrotoxicity. When determining the importance of trough serum levels it is not possible to tell whether elevated predose serum levels are a result of nephrotoxicity or a risk for it. The generally accepted safe trough concentration of gentamicin is lower than 2 mg/ l. [19]

Advanced age has been suggested as a risk factor for aminoglycoside nephrotoxicity, as aging is accompanied by a decreased capacity in renal function and a marked decline of the regenerative response to drug – induced cell injury.[30] In older patient, dosage adjustments are made solely on the serum creatinine value, more sustained serum concentrations may be present , that may be at greater risk of manifesting nephrotoxicity.[19,40]

Male gender has been suggested as a risk factor by unknow reason. [58]

Preexisting kidney disease may be at greater risk of nephrotoxicity, because the kidney reverse is decreased and further damage by the aminoglycoside is exaggerated.[19]

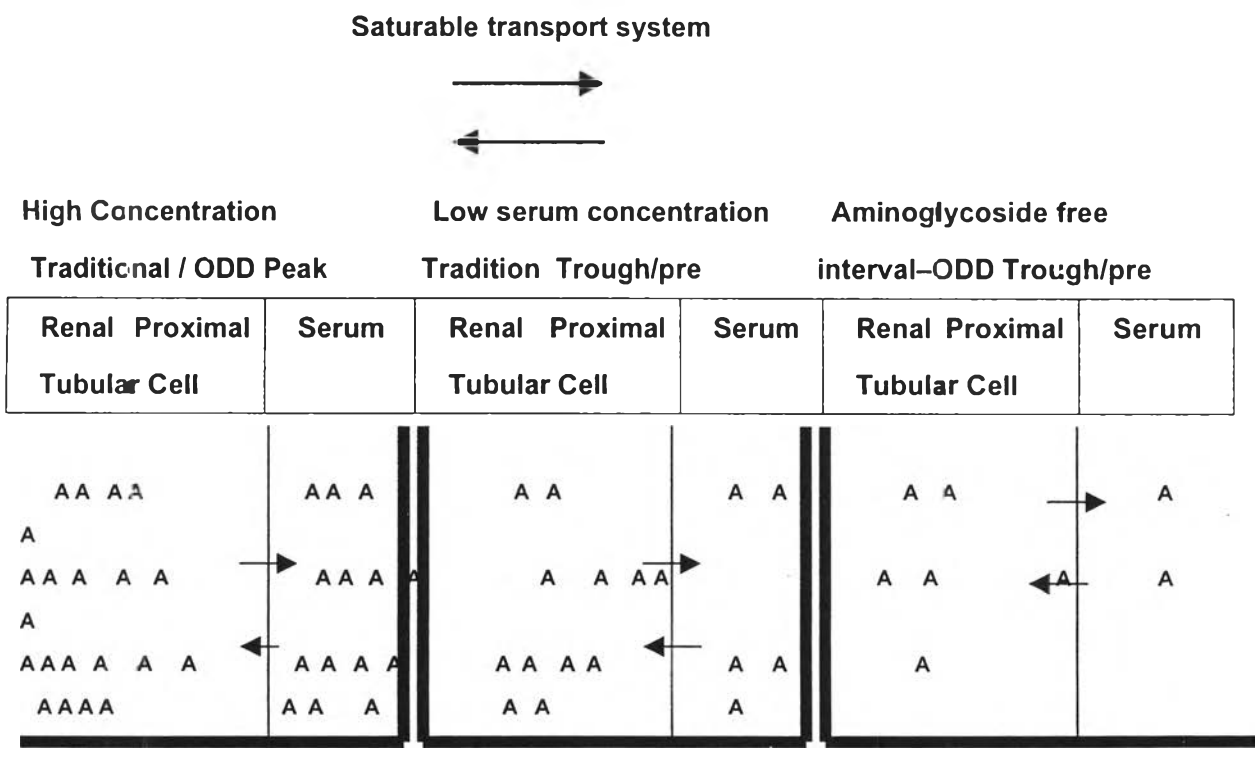
Liver disease or hepatic insufficiency leading to intra – renal vasoconstriction, reduced renal blood flow and stimulation of the renin – angiotensin system is the proposed pathophysiological mechanism. If possible, an aminoglycoside antibiotic should not used to treat infections in patients with chronic liver disease.[19,30,62] The glomerular filtration rate of these patients may be lower than normal level,

although measurement of the serum creatinine in plasma may be present in normal range.[63]

Volume depletion causes a concentration of the urine and may enhance the tissue accumulation of the aminoglycoside in the kidney.[19]

The presence of shock has been associated with an increased risk of nephrotoxicity. In one study in which aminoglycoside serum levels were closely monitored, the effects of shock and aminoglycoside administration were found to be additive.[19] Some studies show that benefits of aminoglycoside ODD[19,22,41,57,60]

Figure 3 Theoretical conceptualization of potential benefit of aminoglycoside ODD[19]



Theoretical conceptualization of potential benefits of aminoglycoside ODD.

Because of the saturable transport system, he amount of drug that enters the renal tubular cell would be the same if the dose used were traditional or the large ODD dose. The

left scenario illustrates this, with the aminoglycoside serum level high as occurs in the peak or postdose period. The center scenario illustrates low serum concentrations, as seen with conventional dosing during the trough period. The amount of drug accumulated intracelluarly is similar to that of the peak period, as there is still aminoglycosides available to continue internal transport. The right scenario illustrates that ODD would create the aminoglycoside – free period. The extremely low serum level of aminoglycoside would allow for the most previously internalized drug to be transported out of the cell and allow for less toxicity.

By administering doses of aminoglycosides in the traditional manner, the internalization system causes accumulation and subsequent toxic effects in the renal cortex. Brush border receptors have a high capacity for internalization of drug. As this system, or the binding, becomes saturated, intracellular renal proximal tubular cell aminoglycoside concentrations increase, and the return of aminoglycosides externally to the proximal tubule remains constant. Because of the finite capacity of this enzyme transport system, the amount of aminoglycoside available for internalization, using the conventional dosing or larger doses, would not affect the intracellular concentrations. With conventional dosing, the constant availability of aminoglycosides never allows the intracellular concentrations to diminish. Hence, when luminal concentrations fall to low or undetectable levels, as in the aminoglycoside free period, the proximal tubular cells are spared further insult and have to process previously internalized drug. This is the theorized advantage of reduced potential for nephrotoxicity with the ODD approach.[19]

Monitoring drug concentrations in plasma is useful, particularly during prolonged and/or high – dose therapy. However, it never has been proven that toxicity can be prevented by avoiding excessive peak or trough concentration of aminoglycosides. In fact experience with once – daily dosing recimens strongly suggests that high peaks (e.g. 15 to 25 mg/l) do not increase toxicity.[40]

2. Otoxicity

The incidence of ooxicity is extremely difficult to determine.[40] Data on the occurrence of ototoxicity depending on the study method, frequency range tested, and other variables.[41] Ototoxicity is directy proportional to the duration and amount of drug given.[3,40]

Both vestibular and auditory dysfunction can follow the administration of any of the aminoglycosides.[40] Although the distinction are not absolute and either or both forms of otoxicity may occur with any of the aminoglycosides, vestibular symtoms are more frequently associated with streptomycin, gentamicin, or tobramicin and auditory symptoms are more frequently associated with amikacin, kanamycin, neomycin or paromomycin.[5,19,40 – 41] Studies of both animals and human beings have documented progressive accumulation of these drugs in the perilymph and endolymph of the inner ear (Hug et at 1983). Accumulation occurs predominantly when concentrations in plasma are high.[40] Ototoxicity from aminoglycosides results from destruction of the sensory hair cells in the cochlea and vestibular labyrinth.[41] Studies in guinea pig exposed to large doses of gentamicin reveal degeneration of the type I sensory hair cell in the central part of the crista ampullaris (vestibular organ) and fusion of individual sensory hairs into giant hairs. Similar studies with gentamicin and tobramycin had demonstrate loss of hair cells in the cochlea of the organ corti (Theopold, 1977).[40–41] With increasing dosage and prolonged exposure, aminoglycosides affect high – frequency (> 4,000 HZ) hearing in cochlear earlier than they affect low - frequency hearing.[19,40,64] While there histological changes correlate with the ability of the cochlear to generate an action potential response to sound, the biochemical mechanism for ototoxicity is poorly understood. Early changes induced aminoglycosides have been in experimental ototoxicity to be reversible by CA^{2+} Once sensory cells lost, however, regeneration does not occur; retrograde generation of the auditory nerve follows, resulting in irreversible hearing loss (Lietman ,1990). It has been suggested that aminoglycosides interfere with the active transport system

essential for the maintenance of the ion balance of the endolymph would lead to alteration in the normal concentrations ions in the labyrinthine fluids, with impairment of nerve conduction, eventually, the electrolyte changes, or perhaps the drugs themselves, damage the hair cells irreversibly. Interest also has centered on interaction of aminoglycosides with membrane phospholipids particularly phosphatidylinositol and its phosphatidylated derivatives, which are the precursors of cell second messengers inositol 1,4,5, - triphosphate and diacyglycerol. [40] These auditory deficits are typically bilateral.[5,64]

Early symptoms of toxicity may appear at the third day of treatment or between the first and second weeks of therapy. Delayed toxicity occurring 10 to 14 days after stopping gentamicin therapy in patients with renal impairment has been reported. Delayed vestibular toxicity presenting 3 and 6 weeks after completion of a course of gentamicin therapy has been reported.[19,40 – 41] Early damage may be reversible but if the antibiotic is continued it may be permanent.[5,19,41]

Eighth cranial nerve damage may be manifested by vestibular symptoms such as dizziness, nystagmus , vertigo and ataxia, and /or by auditory symptoms such as tinnitus roaring in the ears , and varying degrees of hearing impairment.[5,19] Symptoms may be apparent if the patient is bedridden, critically ill, or receiving antiemitic agents.[19]

Loss of high – frequency perception, detectable only by audiometric testing, usually occur before clinical hearing loss.[5] Brain stem auditory evoked response (BARE) has been used to assess eighth nerve and cochlear function in newborn and young infants. Vestibular function can be assessed by electronystagmograms and caloric and balance tests.[19] Adelman, Linder, and Levi 1989 concluded that auditory nerve and brain stem evoked response testing of all gentamicin – treated neonates is unnecessary when risk factors for ototoxicity are absent such as renal insufficiency.[3]

The risk factors associated with the use of the aminoglycoside antibiotics are listed in Table 2.3.[19]

Table 2.3 Risk Factors For Aminoglycoside Ototoxicity

Drug – related	Patient related
Duration of treatment greater than 10 days	Age
Total dose of drug	
Prior exposure to aminoglycosides	Preexisting kidney disease
Concurrent use of diuretic	
High serum level , rough guidelines ,absolute importance of peak or trough levels is not clear	

Duration of treatment greater than 10 days and total dose are risk factors in that the drug can accumulate and remain in contact with ear structures longer and causes damage. Prior exposure to the drugs is important because much of the damage is subclinical and repeated courses, especially when it is given shortly after each other, encourage new or continued damage.

When aminoglycoside therapy is used in conjunction with ethacrynic acid, ototoxicity may be more likely. The use of ethacrynic acid during concurrent aminoglycoside therapy should be avoided. Furosemide can be used safely with an aminoglycoside antibiotic.[19]

The importance of serum levels to ototoxicity is unclear. Ototoxicity may associate with trough plasma concentrations of gentamicin exceeding 4 mg/l for more than ten days (Mawer et al).[15,19,65] Area under the cure (concentration – time) may correlate with toxicity more than serum concentration.

Elderly patients and possibly those with preexisting hearing deficit appear to be at risk of manifesting ototoxicity. Decrease in kidney function with age may

predispose the patient to more sustained serum concentrations of the aminoglycoside, resulting in higher accumulation in the ear. The incidence of ototoxic effects in neonates is lower than in adults. The existence of renal impairment is a risk factor for aminoglycoside ototoxicity. Kidney failure may encourage accumulation of these agents in the ear.[19]

Studies comparing the administration of single total daily dose versus the same dose given in divided dose have found comparable ototoxicity. The result implies the existence of another saturable transport system and suggests that high dose producing high peak serum concentrations should not increase toxicity. These data support the less frequent administration of aminoglycosides and minimization of trough concentration, as they might decrease accumulation in the ear and less ototoxicity.[19,22 – 23,30,34 ,41]

3. Neuromuscular Blockade

Neuromuscular blockade is an unusual toxic reaction of aminoglycisides.[40] Aminoglycosides produce varying degrees of neuromuscular blockade: the order of decreasing potency for blockade is neomycin , kanamycin , amikacin , gentamicin , and tobramycin.[5,40] Although the blockade induced by an aminoglycoside is generally dose related and self – limiting, it may rarely result in respiratory paralysis. Neuromuscular effects are most likely to occur when an aminoglycoside is applied to serosal surfaces can in intrapleural injection or peritoneal instillation 1 or is administered to patients with neuromuscular disease (e.g. , myasthenia gravis) or hypocalcemia or to patients who are receiving general anesthetics , neuromuscular blocking agents , or massive transfusions of citrated blood.[5]

Animal studies indicate that the aminoglycoside inhibit rejunctional release of acetylcholine while also transmitter and CA^{2+} overcomes the effect of the aminoglycoside at the neuromuscular junction, and the intravenous administration of a

calcium salt is the preferred treatment for this toxicity. [40] Drug induced neuromuscular blockade is not easily reversed and its reversibility seems dependent on the severity of the blockade: calcium salts have been used successfully in some cases, but mechanically assisted respiration may be necessary. The efficacy of neostigmine and edrophonium (Inhibitors of cholinesterase) in reversing aminoglycosides – induced neuromuscular blockade is highly variable.

4. Other Untoward Effects

Aminoglycosides have little allergenic potential; both anaphylaxis and rash are unusual. Occasionally, hypersensitivity reactions including rash, urticaria, stomatitis, pruritis, generalized burning, fever, and eosinophilia have occurred in patients receiving an aminoglycoside. Transient agranulocytosis has been rarely reported . Parenterally administered aminoglycosides are not associated with pseudomembranous colitis, probably because they do not disrupt the normal anaerobic flora. Cross – allergenicity among the aminoglycosides has been demonstrated. [5,40]

N. Drug Interactions [39,66]

Table 2.4 Drug interactions of Aminoglycosides

Aminoglycoside Drug Interaction					
Precipitant drug	**Significance Level(**)**	**Onset**	**Severity**	**Effects**	**Management**
Cephalosporin[(a)]	2	Delayed	Moderate	-Nephrotoxicity may be increased. . -Bactericidal activity against certain pathogens may be enhanced.	- Monitor aminoglycoside levels and kidney function closely If renal dysfunction develops, reduce the dosage or discontinue one or both drugs and use alternative agents.

Continue

Aminoglycoside Drug Interaction					
Precipitant drug	**Significance Level(**)**	**Onset**	**Severity**	**Effects**	**Management**
NSAIDS [b]	2	Delayed	Moderate	-Plasma aminoglycoside concentrations may be elevated in premature infants. NSIADs may cause an accumulation of aminoglycosides by reducing GFR.	- Reduce the dose of aminoglycoside prior to starting an NSAID. Base further dosage adjustments on serum aminoglycoside levels and monitoring of renal function.
Penicillins [c]	2	Delayed	Moderate	- Certain parenteral penicillins may in activate certain aminoglycoside.	- Do not mix parenteral aminoglycoside and penicillins in the same solution. Monitor aminoglycoside concentration and renal function. Adjust the dosage as needed.
Vancomycin	4	Delayed	Moderate	- The risk of nephrotoxicity may be increased	- Monitor renal function and serum drug concentrations adjust dosage of aminoglycoside or vancomycin if necessary.
Loop Diuretic Bumetanide Furoxemide Ethacrynicacid Torsemide	4	Rapid	Major	- Auditory toxicity may be increased	- Perform baseline periodic testing and periodic monitoring avoid excessive dose. Reduce dose of one or both drug may be necessary in patient with renal insufficiency

(a) Cefamandole , Cefazolin, Cefonicid, Cefoperazone, Cefotaxime, Cefotetan , Cefoxtin, Cefazoxime , Ceftriaxone , Ceruroxime, Cephalothin, Cephapirin, Cephradine.

(b) Diclofenac , Etodolae , Fenoprofen , Flurbiprofen , Ibuprofen , Indomethacin , Ketoprofen , Ketorolac ,

Meclofenamate , Mefenamic acid , Nabumetone , Naproxen , Oxaprozin , Piroxicam , Sulindac, Tolnetin.

(c) Ampicillin , Penicilling , Methicillin , Mezlocillin , Nafcillin , Oxaxillin , Pipuracillin , Ticarcillin.

** significance Level : Significance level divided in 5 level by severity and documentation

Significance rating	Severity	Documentation
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major or moderate	Possible
5	Minor , any	Possible , Unlikely

II Review of Apgar score

In 1952, a scoring system was devised to evaluate the newborns condition. The score was found to be a measure of the relative handicaps suffered by infants born prematurely, delivered by cesarean section, or subjected to other obstetrical and anesthetic hazards. The condition of each newborn infant was expressed by a score, the sum of five objection signs: heart rate, respiratory efforts, muscle tone, reflex irritability, and color , judged 1 and 5 minutes after delivery.[67 – 70]

Table 2.5 Apgar Score for evaluation of newborn infant

Sign	Score		
	0	1	2
1. Heart rate (Pulse)	Absent	Slow (below 100)	Over 100
2. Respiration (respiratory effort)	Absent	Irregular weak cry; hypoventilation	Good strong cry
3. Muscle tone (activity)	Limp	Some flexion of extremities	Well flexed (Active motion)
4. Grimace reflex Irritability response to stimulation of sole of foot	No response	Some motion	Cry
5. Color	Blue pale	Body pink Extremities blue	Completely pink

Sixty seconds after complete birth of infant (disregarding cord and placenta), the 5 objective signs are evaluated and each given a score of 0, 1, or 2. Score of 10 indicates an infant in best possible condition.

The highest possible score was 10, representing the optimum condition of the infant. The lower scores were generally associated with chemical finding characteristic of asphyxia in the blood obtained by umbilical catheterization. The score was

especially useful in judging the need for resuscitative measures, such as respiratory assistance.

Table2. 6 Severity of Perinatal asphyxia by Apgar score

Severity	Score
Mild	5 – 6 or 7
Moderate	3 – 4
Severe	0 – 2