

## Clinical Pharmacokinetics of Gentamicin in Neonates

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### Abstract

Gentamicin is a bactericidal aminoglycoside antibiotic, it inhibits the protein synthesis. Gentamicin is active against the majority of aerobic gram-negative bacilli such as *Pseudomonas*, *Klebsiella* and *Escherichia coli*. The gentamicin doses are 3 mg/kg once-daily for preterm newborns < 35 weeks of gestation and 4 mg/kg once-daily for newborns > 35 weeks of gestation. The monitoring of gentamicin serum concentration is recommended when infants are treated for 48 hours or more. The gentamicin peak concentration must be at least 8 times the minimum inhibitory concentration (MIC) to be bactericidal and the gentamicin trough concentration must be < 2 µg/ml to avoid ototoxicity and nephrotoxicity.

Once-daily dosing of gentamicin (4 mg/kg), is preferred than twice-daily dose of 2.5 mg/kg gentamicin. A gentamicin loading dose (4 mg/kg), followed by once-daily dosing of 2.5 mg/kg yields safe and target range in neonates. An extended dosing interval of 48-hour (5 mg/kg gentamicin), was compared with twice-daily dose of 2.5 mg/kg gentamicin. Infants in the 48-hour interval and in the twice-daily achieved peak gentamicin concentrations of 9.43 µg/ml and 6.0 µg/ml, respectively, ( $p < 0.001$ ), and trough gentamicin concentrations were 1.08 µg/ml and 1.54 µg/ml, respectively, ( $p < 0.001$ ). The infants born small for gestational age have a reduced gentamicin clearance, and a more prolonged gentamicin half-life than infants born appropriate for gestational age. Patent ductus arteriosus, extracorporeal membrane oxygenation, therapeutic hypothermia, and asphyxia reduce the gentamicin clearance.

**Key Words:** Effects, Gentamicin, Neonates, Pharmacokinetics, Resistance, Toxicity.

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## 1-INTRODUCTION

Gentamicin is a bactericidal aminoglycoside antibiotic, it inhibits bacterial protein synthesis. The higher the concentration, the greater is the rate at which bacteria are killed. Aminoglycosides bind to sites on the 30S subunit of the bacterial ribosome, causing an alteration in the codon: anticodon recognition. This results in misreading of the messenger RNA and hence in the production of defective bacterial proteins. Aminoglycosides penetrate through the cell membrane of the bacterium partly on oxygen-dependent active transport by a polyamine carrier system and they have minimal action against organisms. The bactericidal effect of aminoglycosides is enhanced by agents that interfere with cell wall synthesis (1). Aminoglycosides diffuse through aqueous channels formed by porin proteins in the outer membrane of gram-negative bacteria to enter the periplasmic space. Gentamicin is active against the majority of aerobic gram-negative bacilli such as *Pseudomonas*, *Klebsiella* and *Escherichia coli*.

Gentamicin crosses the placenta, producing fetal levels that are about half of the maternal level, but this has never been known to have caused ototoxicity in the uterus. Absorption from the gut is too limited to disallow maternal use during lactation. Gentamicin is passively filtered unchanged by the glomerulus and concentrated in the urine. As a result, in healthy neonates, the half-life decreases by more than 50% in the first 7-10 days after birth. Renal tubular damage is progressive with time and can even produce a Bartter-like syndrome. Cochlear impairment is uncommon in young children, but gentamicin can cause balance problems as well as high-tone deafness, and these can become permanent if early symptoms go unrecognized. It is important to avoid simultaneous treatment with furosemide and to try to stop treatment after 7-10 days

(2). Aminoglycosides are only effective against many bacteria when their serum level is high enough to be potentially toxic. A high peak level (at least 8 times the minimum inhibitory concentration [MIC]) enhances the drug's bactericidal effect. Gram-negative organisms stop taking up the drug after an hour and only do so again 2-10 hours after (adaptive resistance): therefore, repeat treatment during this time, is ineffective. Serious toxicity is predominantly seen with treatment is longer than 7-10 hours.

When the gentamicin level is  $\leq 1.2$   $\mu\text{g/ml}$  at 22 hours the dosing interval should be once-daily, when the gentamicin level is 1.3-2.6  $\mu\text{g/ml}$  at 22 hours the dosing interval should be 36 hourly, when the gentamicin level at 22 hours is  $\geq 3.6$   $\mu\text{g/ml}$  the dosing interval should be 48 hourly (2). Gentamicin is frequently used in neonates undergoing therapeutic hyperthermia. These neonates typically have renal impairment, close monitoring is mandatory, and dose adjustments are frequently needed. A 4 mg/kg dose and a 36 hourly regimen is reported as best for these neonates. The aim of this study is to review the clinical pharmacokinetics of gentamicin in neonates.

## 2- MATERIALS AND METHODS

### 2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; November 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

### 2-2. Search Terms

The following key words "gentamicin pharmacokinetics neonates", "gentamicin effects neonates", "gentamicin dosage neonates", "gentamicin resistance neonates" and "gentamicin toxicity neonates", were used to search for the

relevant literature. In addition, the books Neonatal Formulary (2), and NEOFAX by Young and Mangum (3), were consulted.

### 3-RESULTS

#### 3-1. Uses

Treatment of infection caused by aerobic gram-negative bacilli (e.g. Pseudomonas, Klebsiella, Escherichia coli). Usually used in combination with a  $\beta$ -lactam antibiotic (3).

#### 3-2. Dose

Give 5 mg/kg intravenously or intramuscularly to infants less than 4 weeks old, and 7 mg/kg to children older than this. Give a dose once every 36 hours in infants less 32 weeks gestation in the first week of life. Give all other infants a dose once every 24 hours unless renal function is poor (2).

#### 3-3. Incompatibility

Amphotericin B, ampicillin, azithromycin, furosemide, imipenem/cilastatin, heparin, indomethacin, mezlocillin, nafcillin, oxacillin, propofol, and ticarcillin/clavulanate (3).

#### 3-4. Peak and trough concentrations of gentamicin in neonates

The peak and trough of gentamicin concentrations were measured in thirty-five neonates aged from birth up to 23 days of life and fifteen infants aged from 35 days of life to 11 months. The peak levels in neonates and infants were  $5.98 \pm 0.48$  and  $4.66 \pm 0.31$   $\mu\text{g/ml}$ , respectively (p-level  $< 0.05$ ). The trough levels in neonates and infants were  $1.06 \pm 0.19$  and  $0.94 \pm 0.23$   $\mu\text{g/ml}$ , respectively. A significantly higher peak concentration of gentamicin was observed in neonates aged under 7 days of life than in those above 7 days of life (4). The authors did not report the gentamicin dose. Koren et al. (5) studied the pharmacokinetics of gentamicin in 48

preterm infants (the gestational age and the body weight were  $31.6 \pm 3.4$  weeks  $1,500 \pm 500$  grams, respectively). The neonates received  $5.2 \pm 0.6$  mg/kg per day. Trough levels were significantly higher in infants less than 1,000 grams receiving 5 mg/kg once-daily than in infants weighing 1,000 to 2,500 grams who received the same dose. Gentamicin half-life was significantly longer in infants under 1,000 grams than in those weighing 1,000-2,500 grams ( $7.9 \pm 1.9$  and  $6.5 \pm 1.9$  hours, respectively, p-level  $< 0.005$ ). These differences could be attributed to lower gentamicin clearance in infants less than 1,000 grams ( $31 \pm 6$  ml/kg/h), and  $39 \pm 8$  ml/kg/h in older infants; p-level  $< 0.005$ ). There was no difference in gentamicin distribution volume between infants less than 1,000 and 1,500 grams ( $0.35 \pm 0.07$  and  $0.38 \pm 0.13$  l/kg, respectively).

A correlation was found between gentamicin clearance and half-life ( $r = 0.57$ ; p-level  $< 0.01$ ). Gentamicin dose in infants less than 1,000 grams should be reduced to 3.5-4 mg/kg once-daily to avoid excessive gentamicin levels which may be associated with nephrotoxicity or ototoxicity.

#### 3-5. Gentamicin serum concentration monitoring in neonates

The pharmacokinetics of gentamicin was studied in 103 neonates (30 were prematures), during the first month of life (6). Gentamicin plasma clearance, half-life, and recommended dose changed exponentially with postnatal age during the first 14 days of life. No significant changes in pharmacokinetic values were noted during the first 3 days of life. The gentamicin dose was 2.5 mg/kg twice-daily. The peak plasma concentration measured within 1 hour after dosing was  $5.33 \pm 0.97$   $\mu\text{g/ml}$ , and the trough gentamicin levels were below 2  $\mu\text{g/ml}$  in 93% of the neonates. These data suggest that 2.5 mg/kg every 12-hours is appropriate in most neonates except for 0-

2-day-old neonates who require 2.5 mg/kg gentamicin every 18-hours. Gentamicin was monitored in 22 severely sick, low-birth-weight newborns on combination therapy with various antibiotics including gentamicin (7). Serum gentamicin concentrations were measured 30 min after, and 3 hours after the infusion of gentamicin. The mean elimination half-life was 5.3 hours. In 7 prematures, possible toxic levels with a mean half-life of 8.3 h; and in 2 prematures, definite toxic levels with a prolonged half-life up to 17 h were observed. Most of the premature infants with possible or definite toxic gentamicin levels were not older than 1 week. This is explained by the immaturity of kidneys and the retention of aminoglycosides. A statistically significant correlation between postnatal age and gentamicin elimination half-life was found, which might be caused by postnatal maturation of the glomerular function. In prematures in the 1st postnatal week Rameis et al. (7) recommend reducing the daily dose by prolonging the dosage interval, e.g., from 12 to 18 h, or reducing the single gentamicin doses. Gentamicin monitoring seems advisable for detecting toxic serum concentrations and accumulation and for revealing an insufficient dosage of this aminoglycoside antibiotic.

Young and Mangum (3) suggest to measure serum gentamicin concentrations when treating for more than 48-hours. Obtain peak concentration 30 min after end of infusion, and trough concentration just prior to the next dose. When treating infants with serious infections or significantly changing fluid or renal status consider measuring the serum concentration once-daily.

### **3-6. Determination of a gentamicin loading dose in neonates**

As neonatal immunity is immature and aminoglycosides have a prolonged elimination half-life in the very-young-population, and the reassessment of the

initial gentamicin dose has become necessary. Semchuk et al. (8) suggested an initial gentamicin dose of 3 mg/kg would be necessary. Younger infants ( $\leq 34$  weeks gestational age), would likely require 4 mg/kg as an initial dose to obtain peak gentamicin concentrations of 6 to 8  $\mu\text{g/ml}$ . One hundred and sixty-six patients less than 12 months of post-natal age were studied. The mean initial dose delivered was 2.41 mg/kg. Younger patients demonstrated larger gentamicin apparent distribution volumes and slower elimination half-lives than did older patients. Initial serum gentamicin concentrations were significantly lower than those seen at steady-state.

Lundergan et al. (9) developed a simplified gentamicin dosing protocol for all neonates using a loading dose followed by once-daily dosing. One hundred and three infants with a postnatal age  $\leq 7$  days received gentamicin. All peak and trough serum gentamicin levels, and markers of potential nephrotoxicity, and ototoxicity were tracked prospectively in consecutive, nonrandomized courses of therapy on a new gentamicin protocol. The pharmacokinetics of gentamicin were compared with data retrieved retrospectively throughout 103 consecutive, nonrandomized courses of therapy and served as controls. Initial measured gentamicin peak levels were  $7.8 \pm 1.1 \mu\text{g/ml}$  in protocol infants versus  $6.1 \pm 1.0 \mu\text{g/ml}$  in control neonates ( $p\text{-level} < 0.05$ ), and trough gentamicin levels were  $0.9 \pm 0.2 \mu\text{g/ml}$  in protocol infants versus  $2.7 \pm 0.6 \mu\text{g/ml}$  in control neonates ( $p\text{-level} < 0.05$ ). Eight-four percent of peak gentamicin concentrations were 5 to 12  $\mu\text{g/ml}$  in protocol neonates and 61% were in the control group. All trough levels in protocol neonates were  $< 2 \mu\text{g/ml}$  compared with 70% of the control neonates ( $p\text{-level} < 0.05$ ). No significant differences were found in any gentamicin levels in low birth weight neonates in the

protocol compared with the control group. The very-low-birth weight (weight < 1,500 grams) protocol neonates had trough serum concentrations < 2 µg/ml in 95% compared with 30% in the control neonates. A loading dose followed by once-daily dosing was shown to result in gentamicin levels in the safe and therapeutic range in all neonates. Delaying the initiation of maintenance once-daily dosing until 36 to 48-hours after the loading dose results in lower trough gentamicin levels in very-low-birth weight neonates.

### **3-7. Once-daily gentamicin dosing in neonates**

Usually, 2.5 mg/kg gentamicin is infused twice-daily, but its large distribution volume and the slow renal clearance suggest that longer dosing intervals would be more appropriate (10). From a previous study, 22% of neonates who received a once-daily gentamicin dosage of 5 mg/kg had unacceptably high trough levels (i.e. > 2 µg/ml). Kiatchoosakun et al. (10) studied 105 neonates (the gestational age was  $\geq 34$  and the birth weight was > 2,000 grams) with clinical features of sepsis, who received 4 mg/kg gentamicin once-daily. Peak (i.e. efficacy), and trough (i.e. toxicity) serum gentamicin concentrations, were collected on day 3 of therapy. On days 1 and 3, nephrotoxicity was evaluated from serum creatinine and ototoxicity by a hearing test. Neonates had mean steady-state peak and trough concentrations of  $7.33 \pm 2.77$  and  $0.99 \pm 0.57$  µg/ml, respectively. The peak serum concentration achieved a therapeutic level > 4 µg/ml in 102 neonates (97%), while 7 infants (6.67%), had a trough level (> 2 µg/ml). No nephrotoxic or ototoxic effects were identified. Gentamicin once-daily at 4 mg/kg/dose in neonates at  $\geq 34$  weeks of gestation achieved appropriate trough levels. The regimen did not increase nephrotoxicity or ototoxicity.

### **3-8. Once-daily compared to twice-daily dose of gentamicin in neonates**

Fifty-eight very-low-birth weight infants (600 to 1,500 grams), received gentamicin for treatment of suspected sepsis during the first week after birth every 48-hours or once-daily (11). Infants in the 48-hours group received 5 or 4.5 mg/kg gentamicin depending on body weight and infants in the once-daily group received 2.5 or 3.0 mg/kg gentamicin. Peak serum gentamicin concentrations after the first dose were significantly higher in the 48-hours group infants than in once-daily group infants ( $8.19 \pm 1.3$  versus  $6.04 \pm 2.2$  µg/ml; p-value = 0.00001). Ninety percent of peak serum concentrations in the 48-hours group were in a higher therapeutic range of 6 to 12 µg/ml as compared with 55% of the once-daily group (p = 0.0005). None of the infants in the 48-hours group had subtherapeutic serum gentamicin concentrations immediately after administration of the first dose as compared with 36% of the infants in the once-daily group (p < 0.005).

Eighteen percent of infants in the once-daily group, continued to have peak serum gentamicin concentrations in the subtherapeutic range even after the third dose. Trough serum gentamicin concentrations were significantly lower in the infants of the 48-hours group than in infants in the once-daily group. However, 9 of 30 (30%) infants of the 48-hours group, had trough serum gentamicin concentration of  $\leq 0.5$  µg/ml at 24-hours after the first dose. The 48-hours dosing schedule of gentamicin given to very-low-birth weight infants during the first week after birth achieved therapeutic serum gentamicin concentrations and higher peak to minimal inhibitory concentration (MIC) ratios for microorganisms in all infants. A dosing interval of 36 hours might be optimal for bactericidal activity and to avoid bacterial growth during prolonged periods of extremely-low-birth weight.

Rao et al. (12) compared the efficacy and safety of once-daily dose to multiple doses per day of gentamicin in suspected or proven sepsis in neonates with 28 days of life. All randomized or quasi randomized controlled trials compared once-daily dose with multiple doses per day of gentamicin concentrations. Eleven studies were included and the number of neonates was 574. All infants in both once-daily dose as well as multiple-daily regimens, showed adequate clearance of sepsis. Once-daily gentamicin regimen was associated with less failure to attain peak level of at least 5 µg/ml and less failure to achieve trough levels of  $\leq 2$  µg/ml compared to multiple-daily regimen. Ototoxicity and nephrotoxicity were not noted with either of the treatment regimens. There is insufficient evidence from the currently available data to conclude whether once-daily is superior compared the multiple-daily dose regimen of gentamicin to treat neonatal sepsis. However, data suggest that pharmacokinetic properties of a once-daily gentamicin regimen is superior to a multiple-daily regimen as it achieves higher peak levels while avoiding toxic trough levels.

Krishnan and George (13) compared the pharmacokinetic profile of gentamicin given a once-daily and twice-daily dose in 18 preterm neonates. The infants were randomly assigned to receive either 4 mg/kg once-daily or 2.5 mg/kg twice-daily gentamicin. Trough and peak levels were measured before and one hour after the dose of 48-hours, respectively. Serum concentration time curves were plotted using the computerized Bayesian forecasting. Optimum therapeutic peak level after the first dose was achieved only with the once-daily gentamicin regimen. After the first dose, the peak levels of gentamicin were  $5.88 \pm 1.10$  µg/ml in the once-day regimen and  $3.88 \pm 0.76$  µg/ml in the twice-day regimen ( $p = 0.001$ ). Once-daily dose of 4 mg/kg gentamicin had

logistic benefit in addition to the obvious pharmacokinetic advantage. Alsaedi (14) compared once-daily dosing regimen to the twice-daily dosing regimen for neonates with body weight  $\geq 2,500$  grams during the first 7 days of life. Fifty full-term infants received gentamicin at a dose of 2.5 mg/kg twice-daily (control group), and 50 term infants received gentamicin at a dose of 4 mg/kg once-daily (protocol group). Peak serum gentamicin levels were higher in the protocol group than in the control group ( $p = 0.001$ ). Ninety-eight percent ( $n = 49$ ), of the protocol group infants and 86% ( $n = 43$ ), of the control group infants had peak serum gentamicin concentration in the therapeutic range. Six percent ( $n = 3$ ), of the protocol infants, compared to 26% ( $n = 13$ ), of the control infants, had trough serum gentamicin levels  $> 2$  µg/ml. Six infants (12%), in the protocol group, versus 20 infants (40%), of the control required a dosing adjustment. Gentamicin doses of 4 µg/ml given once-daily achieved significantly higher peak and safe trough serum concentrations in term infants, compared to the twice-daily regimen of 2.5 mg/kg.

Fifty-four neonates were included and completed the study (15). Twenty-seven neonates were given 2.0-2.5 mg/kg of gentamicin twice-daily while 27 neonates were given 4.0-5.0 mg/kg gentamicin once-daily. The twice-daily dose and the once-daily dose groups had steady-state gentamicin peak concentrations of  $5.94 \pm 1.57$  µg/ml and  $8.92 \pm 1.59$  µg/ml, respectively ( $p < 0.05$ ). The trough concentrations were  $1.44 \pm 0.49$  µg/ml and  $0.90 \pm 0.95$  µg/ml, in the twice-daily and in the once-daily group, respectively ( $p < 0.05$ ). Treatment with a once-daily dose did not present more nephropathy than a twice-daily regimen and had the tendency to have less effect on renal function.

### **3-9. Extended-interval dosing protocol for gentamicin in neonates**

Begg et al. (16), simulated a new dosing protocol for gentamicin in neonates. Clearance, distribution volume and half-life were estimated, and used to produce a new predictive dosing protocol. Gentamicin concentrations from 1,053 individual doses were recorded in the database, 84% achieved the target peak level ( $> 10 \mu\text{g/ml}$ ), and 77% achieved the target trough levels ( $< 1 \mu\text{g/ml}$ ). The number of peak and trough values was improved markedly by prolonging the dose interval. Since the majority of neonates received only a single dose of gentamicin, a new distribution volume-based model was also tested, and performed well. The clearance (l/h) increased, while the distribution volume (l/kg), and the half-life (hours) were decreased in the extended interval dose. Extending the dose interval improves the success in achieving target peak and trough concentrations.

Thingvoll et al. (17), developed and valuated a 48-hour gentamicin dosing regimen for infants born  $< 28$  week's gestation. These authors used previously published pharmacokinetic data and performed Monte Carlo simulations for several gentamicin dosing regimens. On the basis of these simulations, Thingvoll et al. (17), changed dosing for infants born at  $< 28$  weeks to 4.5 mg/kg every 48-hours. These authors then conducted an observational study in 30 infants with this new regimen and compared serum gentamicin levels with 60 control infants who received 2.5 mg/kg once-daily. Infants in the 48-hour group achieved higher gentamicin peak concentration (mean, 9.43  $\mu\text{g/ml}$  versus 6.0  $\mu\text{g/ml}$ , respectively,  $p < 0.001$ ), and lower gentamicin trough concentration (mean, 1.08  $\mu\text{g/ml}$  versus 1.54  $\mu\text{g/ml}$ , respectively,  $p < 0.001$ ). Seven percent of the 48-hour group infants had a gentamicin peak  $< 6 \mu\text{g/ml}$  versus 43% in the once-daily. With a goal for peaks of 6 to 12  $\mu\text{g/ml}$  and for troughs of  $< 1.5 \mu\text{g/ml}$ ,

infants in the 48-hour group required fewer adjustment of their dosing regimens compared with the once-daily group (26.7% versus 78.3%), respectively. Gentamicin given every 48-hours to infants born at  $< 28$  weeks achieves optimal blood concentrations more frequently than once-daily dosing.

Conventional interval dosing is 2.5 mg/kg once-daily and the extended interval dosing is 5 mg/kg every 48-hours. The gentamicin dose is 5.0 mg/kg (18). Twenty infants were in group I (750 to 1,500 grams body weight), 10 infants received gentamicin once-daily, and 10 infants received gentamicin every 48-hours. Twenty infants were in group II (1,500 to 2,000 grams body weight); 11 infants received gentamicin once-daily, and 9 infants received gentamicin every 48-hours. Mean gentamicin peak levels were higher and trough levels were lower in the extended interval dosing compared with the conventional interval dosing, regardless of birth weight (group I,  $p < 0.001$  [peak],  $p = 0.04$  [trough]). Seven infants in the once-daily group, had subtherapeutic peak levels ( $< 5 \mu\text{g/ml}$ ), requiring dose adjustment, in contrast none in extended interval dosing required dose adjustment. Two infants in extended interval dosing had peak levels slightly exceeding the upper limit (12  $\mu\text{g/ml}$ ), and one infant in the once-daily group had a trough level slightly exceeding the upper limit (2  $\mu\text{g/ml}$ ). Overall, seven infants (35%) of the once-daily group had dosage adjustment as compared with only two infants (11%) in the extended interval dosing. The distribution volume was similar in conventional and extended for both group I ( $0.34 \pm 0.21$  l/kg in once-daily versus  $0.21 \pm 0.08$  l/kg in the 48-hours group ( $p = 0.11$ ), and in the group II, the distribution volume was  $0.35 \pm 0.11$  l/kg versus  $0.33 \pm 0.14$  l/kg, respectively ( $p = 0.61$ ). The clearance (l/h/kg) was  $0.021 \pm 0.008$  (once-daily) versus

0.012±0.004 (48-hours) (p= 0.004), in group I, and 0.029±0.005 (once-daily) versus 0.017±0.006 (48-hours) (p= 0.001) in group II. All infants had normal serum creatinine levels (< 1 mg/dl), and urine output (1 to 5 ml/kg/h) throughout the 12-day study period. Three infants (10%) failed the hearing screen in the once-daily and one (5%) in the 48-hours group (p = 0.69). The present findings show that gentamicin extended interval dosing in preterm infants provides higher peaks (therapeutic target of 5 to 12 µg/ml), and lower troughs (< 2 µg/ml) than once-daily dosing.

A total of 113 neonates were included in the study, 43 (38 %) infants were preterm and 70 (62%) were full-term infants (19). The empirical gentamicin dosing regimen was 5 mg/kg every 48-hours (body weight < 1200 grams), 5 mg/kg every 36 hours (body weight 1,200-2,500 grams), 5 mg/kg once-daily (body weight > 2,500 grams), and 5 mg/kg once-daily (term infants). The postnatal age ranged from 1 to 28 days. Target peak and trough gentamicin concentrations were defined as 5 to 10 µg/ml and < 2 µg/ml, respectively. Of 113 infants, 9.73% had a peak serum gentamicin between 10 and 12 µg/ml and 7.08% of the infants achieved peak serum gentamicin concentration ranging between 12.01 and 16.05 µg/ml. None of the infants showed subtherapeutic peak serum gentamicin concentration. Overall, there was 93/113 (82.3%) accuracy with the extended interval dosing guideline followed in the study. Of 113 neonates, 99.1% achieved target trough serum gentamicin concentration (< 2 µg/ml), while 16.8% subjects failed to attain therapeutic peak serum gentamicin concentration. Generally, the study population demonstrated a mean peak concentration of 8.52 µg/ml and a trough concentration of 0.54 µg/ml. The mean gentamicin distribution volume was 0.65 l/kg and the mean half-life was 6.96 hours.

The extended interval dosing used in the present study achieved target concentrations in 82.3% of neonates. There would be no statistical difference in mean peak and trough concentrations across all gestational and body weight groups. Gentamicin is primarily eliminated unchanged by the kidney; any change in renal function will influence the gentamicin elimination rate. Maturation of kidney structure and function is directly proportional to gestational age. Therefore, the preterm infants with fewer glomeruli will possess reduced glomerular filtrating rate and diminished kidney function, resulting in longer gentamicin half-life.

### **3-10. Novel model-based dosing guidelines for gentamicin in preterm and term neonates**

Watterberg et al. (20), studied the pharmacokinetic variables in 100 neonates to evaluate the need for a loading dose. The distribution volume for gentamicin was 0.542±0.205 l/kg. Forty-five percent of the neonates receiving 2.5 mg/kg once-daily did not achieve peak serum concentrations ≥ 5 µg/ml gentamicin. A loading dose of 4 mg/kg would result in a level ≥ 5 µg/ml in 92% of the infants. After this study, a 4 mg/kg loading dose was initiated in the Watterberg et al. (20) team. Peak and trough concentrations at steady-state were compared in 50 infants receiving a loading dose of 4 mg/kg and 50 infants who had not received the loading dose. No significant differences were found in peak or trough concentrations after three or more doses, verifying that a loading dose, does not affect steady-state concentrations. Because gentamicin toxicities are related to accumulation over time, whereas therapeutic efficacy may be related to early attainment of therapeutic peak serum concentration, Watterberg et al. (20) recommend a loading dose of 4 mg/kg in all neonates beginning gentamicin therapy.

### 3-11. Effect of therapeutic hypothermia on gentamicin pharmacokinetics in neonates

Mark et al. (21), investigated whether therapeutic hypothermia in newborns with hypoxic ischemic encephalopathy affects gentamicin pharmacokinetics. Hypoxic ischemic encephalopathy is a syndrome of disturbed neurologic function that occurs secondary to decreased blood oxygenation or diminished brain perfusion as a result of asphyxia event in the perinatal period. Therapeutic hypothermia is the current standard intervention for neonates with hypoxic ischemic encephalopathy. Hypothermia has been associated with a decreased glomerular filtration rate in a number of animal studies, and it may, therefore, impair the elimination of renally excreted drugs in humans. Potential mechanisms of decreased renal clearance include tubular secretion or reabsorption, decreased cardiac output, increased blood viscosity, cold-induced vasoconstriction, blood redistribution, and increased renal renin secretion. Significant differences in gentamicin pharmacokinetics were noted between the therapeutic hypothermia group (n = 16), and the comparator group (n = 7). The elimination rate constant was 0.08/h and 0.11/h, respectively (p < 0.01), the elimination half-life was 9 to 16 hours and 6.56 hours, respectively (p < 0.01). Higher gentamicin trough serum concentrations, were seen in the hypnotic ischemic group (1.68 versus 0.77 µg/ml, respectively; p < 0.01). Therapeutic hypothermia in neonates is associated with alteration in gentamicin pharmacokinetics, reducing gentamicin clearance by 25.5% and increasing trough serum gentamicin levels.

Ting et al. (22), investigated gentamicin pharmacokinetics in neonates with moderate-to-severe hypoxic-ischemia who underwent therapeutic hypothermia. Gentamicin was given at 2.5 mg/kg once-daily. A perceptual > 85% of infants

undergoing therapeutic hypothermia had gentamicin trough concentration > 2 µg/ml at steady-state. In the initial retrospective study, 15 normothermic infants were compared with 19 therapeutic hypothermia infants. There was significant difference in median gentamicin half-life (7.01 versus 9.57 hours, respectively; p < 0.05). A higher proportion 89% of infants in the therapeutic hypothermia group required dosage adjustment versus 53% in normothermic infants. Gentamicin level was measured 12-hours after the first dose and 18/22 (82%) infants undergoing hypothermia had trough gentamicin levels > 2 µg/ml. In these infants the dosing intervals were extended to 18 hours or beyond. Infants with moderate-to-severe hypoxic-ischemic encephalopathy who undergo therapeutic hypothermia exhibit changes in the pharmacokinetic properties of gentamicin. By measuring gentamicin level at 12-hours after the first dose of 2.5 mg/kg, the appropriate dosing interval can be determined and the exposure to toxic gentamicin level can be reduced.

Frymoyer et al. (23), evaluated the pharmacokinetics of gentamicin in 29 full-term neonates with hypoxic ischemic encephalopathy receiving hypothermia to optimize gentamicin dosing strategy in this population. A population based pharmacokinetic model was developed using nonlinear mixed-effects modeling (NONMEN). A one-compartment model best described the available gentamicin concentration data. For the typical study neonate (birth weight 3,300 grams and serum creatinine 0.9 µg/ml), the clearance was 0.034 l/h/kg and the distribution volume was 0.52 l/kg. A prolonged 36-hours dosing interval will be needed to achieve target gentamicin trough concentrations in this population. **Table.1** summarizes the peak and trough gentamicin concentrations of gentamicin with the regimens of 3, 3.5, 4.0, 4.5 and 5.0 mg/kg gentamicin in neonates with

hypoxic ischemic encephalopathy receiving hypothermia.

### **3-12. A simplified protocol for the determination of gentamicin pharmacokinetics in neonates**

Hoff et al. (24), determined the pharmacokinetic outcomes of a simplified, weight-base gentamicin dosing protocol for critically ill neonates. A total of 644 critically ill neonates less than 7 days postnatal age and weighing < 1,250 grams without evidence of renal dysfunction were enrolled. A gentamicin dose of 3.96 mg/kg was administered every 48-hours. Mean gentamicin peak and trough concentrations were 9.38 µg/ml and 1.00 µg/ml, respectively. With the use of the protocol, 361 neonates (56.1%) achieved gentamicin peak plasma concentrations in the range defined as successful and 610 neonates (94.7%) achieved successful trough concentrations. The mean gentamicin apparent distribution volume and half-life were 0.48 l/kg and 8.31 hours, respectively. This simplified, weight-based, extended-interval gentamicin dosing protocol for critically ill neonates was effective in achieving therapeutic peak and trough plasma concentrations of gentamicin in most of the patients.

Gentamicin pharmacokinetics were studied in 195 neonates using a dosing protocol (25). Administered doses, gentamicin concentration measurements, and recorded times were used to calculate each infant's clearance, distribution volume, elimination rate constant, and half-life. The performance of 15 dosing protocols, 6 previously published, and 9 developed on the basis of the study, was evaluated using the pharmacokinetic data. The mean  $\pm$  standard deviation (SD) clearance, distribution volume, elimination rate constant, and half-life were  $0.107 \pm 0.032$  l/hr,  $0.45 \pm 0.11$  L/kg, and  $7.19 \pm 2.64$  hours, respectively. Body weight, urine output, gestational age, and post-conceptual age, had the highest correlation with the

pharmacokinetic values. The published protocols produced the greatest percentage of neonates with peaks from 5 to 10 µg/ml and troughs of < 2 µg/ml. The devised protocols tended to perform poorly in producing troughs between 1 and 2 µg/ml, yet performed comparatively well in providing therapeutic peaks from 5 to 10 µg/ml.

### **3-13. Effect of neonatal development on gentamicin pharmacokinetics**

Rocha et al. (26), evaluated the performance of 8 different sets of gentamicin population pharmacokinetic parameters, regarding the potential implementation in clinical pharmacokinetic software as prior information. The study involved 49 infants of  $31.3 \pm 4.1$  weeks of gestational age receiving gentamicin, and for whom peak and trough concentrations were measured. The analysis showed clearance = 0.036 l/h/kg (< 34 weeks of gestational age), or 0.051 l/h/kg ( $\geq$  34 weeks of gestational age;  $p < 0.05$ ), and the distribution volume = 0.5 l/kg ( $\geq$  37 weeks of gestational age), or 0.4 l/kg (> 37 weeks of gestational age,  $p < 0.05$ ). The adoption of the previously mentioned set of parameters as population estimates seems to be the best option, bearing in mind the obtained results. However, Rocha et al. (26), strongly believe that pharmacokinetic parameters determination of gentamicin should be carried out whenever possible in order to improve the rationale and cost-effectiveness of therapy.

Sixty-eight preterm infants of 24 to 34 weeks of gestation and 600 to 3,100 grams birth weight in their first week of life, undergoing routine therapeutic drug monitoring of their gentamicin serum levels were enrolled in the study (27). Gentamicin pharmacokinetic parameters were determined through non-linear regression analysis by using a single-compartment open model. Gentamicin clearance depended on gestational age

with a cutoff at 30 weeks, which allowed the division of the overall population into two subsets (< 30 weeks of gestational age and between 30-34 weeks of gestational age). The younger neonates (< 30 weeks of gestational age), showed a lower gentamicin clearance of 0.0288 l/h/kg and 0.0340 l/h/kg (30-34 gestational ages) ( $p < 0.05$ ). The infants with a gestational age of < 30 gestational weeks have a slightly higher distribution volume of 0.464 l/kg than 0.435 l/kg in infants of 30-34 gestational weeks, and a longer half-life was 11.17 hours than 8.88 hours, respectively, ( $p < 0.05$ ). On the basis of the pharmacokinetic parameters obtained, Rocha et al. (27), suggest loading doses of 3.7 and 3.5 mg/kg for the two subgroups of neonates (< 30 weeks and 30-34 weeks of gestational age), respectively. The appropriate maintenance doses in accordance with the characteristics of neonates should be 2.8 mg/kg and 2.6 mg/kg every 18 hours for neonates < 30 weeks and between 30-34 weeks of gestational age, respectively.

### **3-14. Developmental pattern of gentamicin pharmacokinetics in very low birth weight sick infants**

Pharmacokinetic studies were carried out in 15 very-low-birth weight infants (28). All infants received two courses, but only 6 required three courses of gentamicin. Gentamicin daily dosage was  $2.0 \pm 0.2$  mg/kg once-daily for the first and second courses and 2.5 mg/kg every 12-hours for the third courses. Gentamicin dosage was adjusted to maintain serum peak gentamicin concentrations of 4-8  $\mu\text{g/ml}$  and trough concentrations of 0.5-2  $\mu\text{g/ml}$ . Gentamicin clearance and the elimination rate constant were calculated based on postnatal age of  $\leq$  to 7 (I) days, 8-30 (II) days, and  $\geq$  to 31 (III) days. The mean body weight and the gestational age were 1,002 grams and  $28.4 \pm 1.5$  weeks, respectively. Mean postnatal age for the starting gentamicin therapy was the first

day,  $19 \pm 9$  and  $68 \pm 26$  days, respectively. Mean serum gentamicin peak and trough concentrations were  $5.9 \pm 1.1$  and  $1.6 \pm 0.6$   $\mu\text{g/ml}$  for the first,  $5.7 \pm 1.2$  and  $1.3 \pm 0.6$   $\mu\text{g/ml}$  for the second,  $5.1 \pm 0.8$  and  $1.1 \pm 0.6$   $\mu\text{g/ml}$  for the third course of therapy, respectively. Mean apparent distribution volumes of gentamicin were  $0.53 \pm 0.10$  l/kg for the first and  $0.50 \pm 0.11$  l/kg for the second and for the third courses, respectively. Mean clearances of gentamicin for the chronologic age groups were  $6.4 \pm 1.9$ ;  $7.6 \pm 3.2$ ;  $7.9 \pm 3.2$ ;  $24.1 \pm 8.0$  ml/min/1.73 m<sup>2</sup>, respectively. Serum creatinine concentrations were  $1.33 \pm 0.4$ ,  $1.2 \pm 0.6$  and  $0.6 \pm 0.4$  mg/dl, respectively. There were no statistically significant differences for serum creatinine concentration and gentamicin clearance between the third course and the first and second courses. Gentamicin clearance closely correlated with creatinine clearance ( $r = 0.99$ ;  $p < 0.001$ ). This study shows that during the first month of life, very-low-birth weight sick infants still have decreased renal function and poor gentamicin clearance. Gentamicin should be given once-daily and the dose should be adjusted based on individual infant serum gentamicin levels.

### **3-15. Optimizing of gentamicin use in neonates during the first week of life**

Seventy-three neonates were enrolled in the study (29). Preterm neonates were the predominant group (60%), and the prevalence of extremely-low-birth weight was higher in this group. Eleven infants (15%) suffered from sepsis; eight of them were preterm. The extremely-low-birth weight had a gestational age and a body weight of < 29 weeks and < 1,000 grams, respectively. The gentamicin dose and interval between doses were 5 mg/kg every 48-hours, respectively. Very-low-birth weights had a gestational age and body weight of 30-33 weeks and 1,000-1,500 grams, respectively, and the gentamicin dosage was 4.5 mg/kg every 36 hours.

Low-birth-weights had a gestational age and birth weight of 34-36 weeks and > 1,500-2,500 grams, respectively. The normal body weights had a gestational age of 36-38 weeks and a birth weight of 2,500-4,000 grams, respectively, and the gentamicin dosage was 4 mg/kg once-daily. **Table.2** summarizes the gentamicin peak and trough concentrations and **Table.3** shows the pharmacokinetic parameters of gentamicin in four groups of neonates. Out of 73 infants, 53 (73%), had a peak level within the therapeutic range (6 - 12 µg/ml), 18 infants (25%) had a peak level (> 12 µg/ml), and 9 (12%), had potentially toxic trough levels (> 2 µg/ml).

Neonates with extremely-low-birth-weight had significantly ( $p < 0.05$ ) longer half-life. Neonates with documented sepsis had significantly ( $p < 0.05$ ) larger mean distribution volume ( $0.49 \pm 0.069$  l/kg) than non-septic neonates who had a distribution volume of  $0.042 \pm 0.013$  l/kg. The incidence of potentially toxic trough levels was clearly higher in infants who received 4 mg/kg gentamicin once-daily. All peak concentrations were within the therapeutic range and none showed trough levels > 2 µg/ml. Gentamicin dose of 4.5 mg/kg every 36 hours is recommended as a simple empirical regimen during the first week of life for neonates with normal or low-birth-weight and every 48 hr for those with extremely-low-birth weight.

### **3-16. Effect of extracorporeal membrane oxygenation on gentamicin pharmacokinetics in neonates**

Cohen et al. (30), evaluated the effects of extracorporeal membrane oxygenation on the pharmacokinetics of gentamicin in 18 infants who received gentamicin for possible sepsis. Twelve of these infants continued to receive gentamicin after extracorporeal membrane oxygenation had been discontinued. The distribution volume of gentamicin in newborns receiving extracorporeal membrane oxygenation was larger ( $0.58 \pm 0.04$  l/kg)

than that of infants where the extracorporeal membrane oxygenation had been discontinued ( $0.45 \pm 0.02$  l/kg;  $p=0.02$ ). The clearance of gentamicin in infants undergoing extracorporeal membrane was  $42 \pm 3$  ml/kg/h compared with  $57 \pm 4$  ml/kg/h in those infants off extracorporeal membrane oxygenation ( $p=0.003$ ). The elimination half-life in neonates receiving extracorporeal membrane oxygenation was  $10.0 \pm 0.7$  hours compared with  $5.7 \pm 0.4$  hours in infants off extracorporeal membrane oxygenation ( $p < 0.0001$ ). Neonates undergoing extracorporeal membrane oxygenation demonstrate a higher distribution volume of gentamicin, a lower clearance, and consequently a longer half-life for gentamicin. Cohen et al. (30) conclude that gentamicin, and probably other aminoglycosides, should be given at dose rates about 25% lower than usual and at longer dosing intervals in patients undergoing extracorporeal membrane oxygenation therapy.

The primary diagnosis of 29 infants enrolled in the study included one or more of the following: meconium aspiration syndrome, pneumonia, diaphragmatic hernia, sepsis, and respiratory distress syndrome (31). The gentamicin dose was 2.5 mg/kg every 18 hours. Mean  $\pm$  SD gestational age and birth weight were  $39.2 \pm 2.7$  weeks and  $3,350 \pm 710$  grams, respectively. The mean gentamicin peak concentration was 6 µg/ml. Serum creatinine concentration ranged from 5 to 66 mg/dl. Urine output during the course of gentamicin therapy ranged from 0 to 7.9 ml/kg/hour. The pharmacokinetic parameters were: rate constant elimination =  $0.072 \pm 0.02$  hours<sup>-1</sup>, half-life =  $10.36 \pm 2.95$  hours, distribution volume =  $0.668 \pm 0.2$  l/kg, and the total body clearance =  $0.05 \pm 0.02$  l/kg/h. Southgate et al. (32), determined the pharmacokinetic parameters of gentamicin in 10 infants on extracorporeal membrane oxygenation.

Pharmacokinetic parameters were determined by using a two-compartment model. These authors demonstrated a mean steady-state distribution volume of  $0.51 \pm 0.11$  l/kg, a value similar to that in previous studies of full-term infants. The elimination half-life was found to be prolonged (mean  $\pm$  SD =  $9.55 \pm 4.4$  hours). The creatinine level in the plasma of infants was found to be a statistically accurate predictor of elimination half-life.

### **3-17. Effect of patent ductus arteriosus on the pharmacokinetics of gentamicin in neonates**

Williams et al. (33), determined the effect of patent ductus arteriosus on the pharmacokinetics of gentamicin in neonates < 36 week old. All infants received a gentamicin loading dose, and had gentamicin concentrations measured at 2 and 12-hours after the gentamicin administration. A total of 322 courses of gentamicin were administered (patent ductus arteriosus, n = 106; controls, n = 216). Gentamicin clearance decreased in the patent ductus arteriosus group versus the control group (40.02 versus 44.73 ml/kg/h, respectively;  $p < 0.0108$ ). The distribution volume was larger for patent ductus arteriosus infants (0.61 l/kg) than for controls (0.54 l/kg;  $p < 0.0002$ ). Gentamicin dosing should be altered in neonates with patent ductus arteriosus to reflect the impact of higher distribution volume and lower clearance. When the gentamicin distribution volume exceeds 0.7 l/kg, it may be of predictive value for the presence of patent ductus arteriosus.

Watterberg et al. (34), studied the effect of patent ductus arteriosus on the pharmacokinetics of gentamicin in very-low-birth-weight neonates. Twenty-four neonates weighing < 1,500 grams were compared with 16 neonates without patent ductus arteriosus. Infants with patent ductus arteriosus had significantly larger distribution volume ( $0.64 \pm 0.20$  versus

$0.41 \pm 0.08$  l/kg, respectively;  $p < 0.001$ ), and serum half-life ( $8.49 \pm 2.69$  versus  $6.23 \pm 1.92$  hours, respectively;  $p < 0.01$ ). The total body clearance was not significantly different between the two groups ( $56 \pm 20$  ml/kg/h in infants with patent ductus arteriosus versus  $50 \pm 24$  ml/kg/h in control neonates). In addition, 7 neonates were studied before and after patent ductus arteriosus. The apparent distribution volume fell in every case ( $p = 0.02$ ), whereas the clearance and the half-life of gentamicin were not different in the two groups of neonates. These findings suggest that patent ductus arteriosus increases extracellular fluid volume, but does not affect glomerular filtration rate adversely.

A patent ductus arteriosus may influence renal and hepatic blood flow and hence pharmacokinetics of drugs in neonates compared to infants with closed ductus arteriosus. Twenty-four neonates (12 with patent ductus arteriosus and 12 neonates with closed ductus arteriosus), were treated with gentamicin (35). Data were analyzed using the standard two-stage approach and an iterative 2-stage Bayesian population analyses approach. Both types of analyses showed no significant differences between both populations for gentamicin clearance. The distribution volume tended to be larger and elimination rate tended to be smaller in neonates with patent ductus arteriosus. Multiple regression analysis showed for both populations significant correlates between total body clearance and body weight ( $p$ -level  $< 0.0001$ ), or gestational age ( $p < 0.0001$ ). Although neonates with a patent ductus arteriosus may have small differences in gentamicin pharmacokinetics compared to neonates with a closed ductus arteriosus, this is not relevant for clinical practice taking the variability within that population into account.

### **3-18. Effect of renal function development on gentamicin disposition in neonates**

The steady-state pharmacokinetics, renal function and quantitative  $\beta$ 2-microglobulin excretion were prospectively evaluated in 22 very-low-birth-weight infants (700-1,470 grams of birth weight and 25-33 weeks of gestational age), receiving 2.4 mg/kg gentamicin at randomly assigned 12-18-hour dosing intervals (36). Gentamicin trough concentrations were significantly lower in only those infants greater than 1,000 grams birth weight on the 18-hour schedule ( $p < 0.05$ ). Strip Analysis of gentamicin disposition at steady state revealed a biexponential function with elimination half-life (mean  $\pm$  standard error of mean (SEM) =  $9.78 \pm 0.86$  hours, plasma clearance =  $0.64 \pm 0.06$  ml/kg/min and distribution volume =  $0.50 \pm 0.03$  l/kg). Serum creatinine at steady-state correlated with gentamicin half-life ( $p < 0.01$ ), and gentamicin plasma clearance ( $p < 0.01$ ). Gentamicin trough levels were persistently  $> 2.0$   $\mu$ g/ml. Renal function matured normally as serum creatinine at steady-state correlated with gentamicin half-life ( $p < 0.01$ ) and gentamicin plasma clearance ( $p < 0.001$ ). Despite the frequent occurrence of gentamicin trough levels persistently  $> 2.0$   $\mu$ g/ml, renal function matured normally as serum creatinine concentration progressively decreased ( $p < 0.001$ ) and creatinine clearance progressively increased ( $p < 0.001$ ) with advancing conceptional age. Urinary excretion of  $\beta$ 2-microglobulin, thought to be a marker of proximal tubular damage from gentamicin, did not correlate with elevated gentamicin trough levels, and was in fact lower in those infants with the highest gentamicin trough levels ( $p < 0.001$ ). Nephrotoxicity was suspected in only 2 infants both of whom had additional renal insult during the first few days of life. Despite the frequent occurrence of elevated gentamicin

trough levels and prolonged elimination half-life in these very-low-birth weight infants, their renal function matured normally throughout therapy and nephrotoxicity from gentamicin, as evidenced by  $\beta$ 2-microglobulinuria, did not occur.

Brion et al. (37) evaluated the relationship between gentamicin pharmacokinetics and glomerular filtration rate in newborn infants to estimate the appropriate interval of gentamicin administration in neonates with renal insufficiency. Gentamicin half-life could be predicted from plasma creatinine concentration ( $r = 0.78$ ); the prediction was minimally but significantly increased ( $r = 0.81$ ) by adding post-conceptional age to a multiple regression analysis. Infants with a post-conceptional age of 29 weeks or more and a plasma creatinine concentration of 1 mg/dl or more had significantly greater trough and peak gentamicin levels than those with a plasma creatinine concentration less than 1 mg/dl. If gentamicin is indicated in a patient with renal insufficiency, the interval of administration should be 2-3 gentamicin half-life, which can be estimated from the plasma creatinine concentration (gentamicin half-life =  $2.0 + 7.7$  plasma creatinine concentration). The interval can then be adjusted according to peak and trough gentamicin levels.

### **3-19. Gentamicin pharmacokinetics in neonates small-for-gestational age and in neonates appropriate-for-gestational age**

Lulic-Botica et al. (38), compared gentamicin pharmacokinetics among neonates born small-for-gestational age and neonates with appropriate-for-gestational age. These authors further compared gentamicin pharmacokinetics in subgroups of appropriate-for-gestational age and small-for-gestational age neonates born preterm and term and treated within and after the initial week of age. Steady-

state peak and trough serum gentamicin concentrations were used to calculate the clearance, elimination rate constant, distribution volume, and half-life in 236 infants who received a mean gentamicin dose of 3.1 mg/kg in infants small-for-gestational and 3.3 mg/kg in infants appropriate-for gestational age. The intervals between doses were  $\geq 48$ -hours. **Table.4** summarizes the vital and pharmacokinetic parameters in two groups of neonates. The birth weight and the elimination rate constant were lower in small-for-gestational infant age whereas the gentamicin half-life was longer in these infants than in infants with appropriate-for-gestational age.

### **3-20. Gentamicin disposition in asphyxiated newborns**

Friedman et al. (39), investigated the effects of changes in renal function on gentamicin disposition following perinatal asphyxia. Gentamicin pharmacokinetics, renal function, mean arterial pressure, and five-min Apgar scores were determined in 80 preterm infants admitted to two neonatal intensive care units (NICU) over an 18 month period. A 2.5 mg/kg dose of gentamicin was infused intravenously over 20 to 30 min in a retrograde fashion. For the asphyxiated infants, gentamicin half-life was prolonged and urine output decreased with a significant correlation ( $r = -0.66$ ;  $p < 0.05$ ). Gentamicin clearance and urine output in the asphyxiated group correlated with mean arterial pressure ( $r = 0.67$ ;  $p = 0.07$ ). In non-asphyxia infants no such correlation was seen. Friedman et al. (39), suggest that gentamicin concentrations should be closely monitored in asphyxiated newborns who demonstrate compromised renal function.

### **3-21. Resistance to gentamicin in neonates**

A total of 130 neonates with sepsis who were found to be blood culture positive were enrolled. Culture/sensitivity was

done, isolated organisms identified and their sensitivity/resistance was noted against different antibiotics. Data were arranged in terms of frequency and percentage (40). Out of 130 culture proven cases, gram-negative bacteria were found in 71 (54%) cases and gram-positive bacteria were found in 59 (45.6%) cases. *Staphylococcus aureus* was the most common bacteria found in 35 (26.9%) cases followed by *Escherichia coli* in 30 (23.1%) cases. Gentamicin was resistant in 55.1% cases of gram-negative bacteria.

Gentamicin is commonly used in the management of neonatal infections (41). Development of adaptive resistance is typical for aminoglycosides and reduces the antibacterial effect. There is, however, a lack of understanding of how this phenomenon influences the effect of different dosing schedules. Mohamed et al. (41), developed a pharmacokinetic-pharmacodynamic (PK-PD) model that described the time course of the bactericidal activity of gentamicin and its adaptive resistance and to investigate different dosing schedules in preterm and term newborn infants based on the developed model. In vitro time-kill curve experiments were conducted on a strain of *Escherichia coli* (MIC of 2  $\mu\text{g/ml}$ ). The gentamicin exposure was either constant (0.125 to 16 mg/liter), or dynamic (simulated concentration-time profiles in a kinetic system with peak concentrations of 2.0, 3.9, 7.8, and 16  $\mu\text{g/ml}$  were given as single doses or as repeated doses every 6, 12, or 24 h). Semimechanistic pharmacokinetic-pharmacodynamic models were fitted to the bacterial counts in the nonlinear mixed effects modeling (NONMEM) program. A model with compartments for growing and resting bacteria, with a function allowing the maximal bacterial killing of gentamicin to reduce with exposure, characterized both the fast bactericidal effect and the adaptive resistance. Despite a lower peak

concentration, preterm neonates were predicted to have a higher bacterial killing effect than term neonates for the same per-kg dose because of gentamicin's longer half-life. The model supported an extended dosing interval of gentamicin in preterm neonates, and for all neonates, dosing intervals of 36 to 48 h were as effective as a 24-h dosing interval for the same total dose.

### **3-22. Ototoxicity and nephrotoxicity following gentamicin administration to neonates**

To assess the risk of gentamicin toxicity and the potential number of neonates exposed annually to this risk, through treatment with WHO-recommended first line antibiotics (gentamicin with penicillin) for 6.9 million neonates with possible serious bacterial infection (42). Eleven studies (946 neonates), were included (nine randomized controlled trials and two prospective cohort studies). Six trials reported consistently measured ototoxicity outcomes in neonates treated with gentamicin, and the pooled estimate for hearing loss was 3%. Nephrotoxicity could not be assessed due to variation in case definitions used. Estimates of the number of neonates potentially affected by gentamicin toxicity were not undertaken due to insufficient data. Given a wider scale-up of outpatient-based and lower-level of possible serious bacterial infection, improved data are essential to better assess the risk from neonatal gentamicin treatment without assessment of blood levels, to maximize benefit and reduce harm.

Davies and Cartwright (43), determined the incidence of toxic trough serum gentamicin levels in neonates in the first week of life, with different dosage intervals. A trough serum gentamicin  $\geq 1.5$   $\mu\text{g/ml}$  was considered toxic. One hundred and seventy infants met the study criteria. All 21 infants in group one (24-29

gestational weeks) received gentamicin once-daily. Sixteen (76%) infants had toxic trough serum gentamicin levels. In group two (30-34 gestation weeks), 8 infants had gentamicin every 12-hours and all had toxic trough serum gentamicin levels. Fourteen infants had gentamicin every 18 hours, and 13 (93%) had toxic trough serum gentamicin levels. Sixty-one infants had gentamicin once-daily, and 25 (41%) had toxic trough serum gentamicin levels. The differences in proportions with toxic levels were statistically significant. In group three (the gestational age was  $> 35$  weeks), 29 infants had gentamicin every 12-hours and 25 infants (86%) had toxic trough serum gentamicin levels. Six infants had gentamicin every 18 hours and 2 (33%) had toxic serum gentamicin levels. The differences in proportions comparing infants having gentamicin every 12-hours with those having gentamicin once-daily were statistically significant. A starting gentamicin dosage interval of 12-hour in infants of any gestational age, or a starting dosage interval of once-daily for infants  $< 30$  gestational age or greater, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of once-daily.

Kent et al. (44), described clinical studies of neonatal gentamicin that report ototoxicity. Overall 577 premature and term neonates underwent a range of audiometry assessments and 22 (3.8%) neonates with hearing impairment were identified. There was no clear relationship between peak and trough gentamicin levels and ototoxicity. While the majority of studies report no effect of gentamicin on plasma creatinine (44); a negative effect was seen in three studies, in particular in the low birth weight or premature cohorts. It is likely that some of these studies present an overestimate of the frequency of hearing loss, as there was no later verification of hearing status following an

initial hearing loss fail. Additionally, they include infants who received prolonged aminoglycoside courses (often 30 days), which does not represent current practice. While the majority of studies report no effect of gentamicin on plasma creatinine, a negative effect [three studies (9, 45, 46)] was seen, in particular in the low-birth

weight or premature cohorts infants. There was no consistent association between increased urinary electrolytes and gentamicin therapy between studies. Changes in urinary excretion of these biomarkers are transient, returning to baseline within days of the end of therapy treatment.

**Table-1:** Predicted gentamicin peak and trough concentrations (µg/ml) at steady-state from 5,000 Monte Carlo simulations with various dosing regimens. [The figures are the median, by Frymoyer et al. (23)]

Dosing regimen	3 mg/kg		3.5 mg/kg		4 mg/kg		4.5 mg/kg		5 mg/kg	
	Peak	Trough	Peak	Trough	Peak	Trough	Peak	trough	Peak	Trough
24 hours interval	7.1	1.4	8.2	1.6	9.4	1.8	10.6	2.1	11.8	2.3
36 hours interval	6.3	0.5	7.4	0.6	8.4	0.7	9.5	0.8	10.5	0.9
48 hours interval	6.0	0.5	7.4	0.6	8.0	0.3	9.0	0.3	10.0	0.4

**Table-2:** Peak and trough concentrations of gentamicin in neonates (% of total samples) in view of dosing regimen. [The number of neonates is 73, by Ali et al. (29)]

Dosing regimen	Peak concentrations (µg/ml)				Trough concentrations (µg/ml)	
	< 6	6 - < 8	>8 - 12	> 12	0 - 2	> 2
4 mg/24-hours	2.4	9.7	70.6	17.07	80.4	19.5
4.5 mg/36 hours	0	7.6	53.8	38.4	96	3.8
5 mg/48-hours	0	17	66	17	100	0

**Table-3:** Pharmacokinetic parameters of gentamicin classified according to the birth weight. The number of neonates is 73. [The figures are the range or Mean  $\pm$  SD (29)]

Variables	ELBW (n = 8)	VLBW (n = 11)	LBW (n = 28)	Normal Birth weight (n = 26)
Birth weight range (grams)	0.64 - 0.980	1.1 - 1.49	1.46 - 2.38	2.51 - 4.2
Distribution volume (l/kg)	0.45 $\pm$ 0.16	0.429 $\pm$ 0.261	0.42 $\pm$ 0.14	0.41 $\pm$ 0.12
Coefficient of variation (%)	36	60	33	30
Clearance (l/kg/h)	0.035 $\pm$ 0.008	0.04 $\pm$ 0.007	0.036 $\pm$ 0.005	0.034 $\pm$ 0.003
Coefficient of variation (%)	23	17.5	14	10
Half-life (hours)	11.45 $\pm$ 4.9*	7.9 $\pm$ 2.3	8.7 $\pm$ 2.5	9.17 $\pm$ 3.48
Coefficient of variation (%)	42	30	30	37

\*Significantly different  $p < 0.05$ ; ANOVA; ELBW = extremely low birth weight; VLBW = very low birth weight; LBW = low birth weight; SD= standard deviation.

**Table-4:** Comparison of median interquartile range (IQR) baseline, and TDM parameters between groups of small-for-gestational age (SGA), and appropriate-for-gestational age (AGA) infants who underwent gentamicin TDM at  $\leq 7$  days of life (38)

IQR	SGA (n = 29)	AGE (n= 135)	P-value
Gestational age (weeks)	30 (27-38)	32 (27-38)	0.694
Birth weight (grams)	770 (545-2,312)	1,850 (1,030-2,980)	0.001
Gentamicin dose (mg/kg/dose)	3.1 (3.0-3.4)	3.3 (2.9-3.5)	0.82
Age at TDM (days)	4 (3.5-4)	4 (3-5)	0.317
Weight at TDM (grams)	860 (535-2,300)	1,780 (920-2,940)	0.001
Kel (hours <sup>-1</sup> )	0.069 (0.050-0.081)	0.081 (0.064-0.106)	0.017
Half-life (hours)	10 (8.5-14.1)	8.6 (6.9-10.8))	0.008
Clearance (ml/kg/min)	0.58 (0.41-0.84)	8.6 (0.57-0.90)	0.036
Distribution volume (l/kg)	0.5 (0.4-0.67)	0.5 (0.42-0.62)	0.969
Peak concentration ( $\mu$ g/ml)	7.7 (5.5-8.5)	7.6 (6.2-8.6)	0.645
Trough concentration ( $\mu$ g/ml)	1.2 (1.1-1.6)	1.1 (0.8-1.6)	0.278
Serum creatinine (mg/gl)	0.8 (0.5-1.1)	0.8 (0.6-0.9)	0.524

#### 4-DISCUSSION

Gentamicin is a bactericidal aminoglycoside antibiotic and is active against the majority of aerobic gram-negative bacilli. *Pseudomonas*, *Klebsiella*, and *Escherichia coli* are killed by gentamicin (3). Peak and trough gentamicin concentrations range in wide intervals in neonates (4), and Young and Mangum (3) suggest monitoring the serum gentamicin concentrations, when infants are treated for 48-hours or longer. Gentamicin half-life is higher in neonates weighing < 1,000 grams than in infants weighing 1,000-2,500 grams ( $p < 0.005$ ) (5). A loading dose of 4 mg/kg is necessary in infants with a gestational age  $\leq 34$  weeks to achieve initial serum concentrations of 6 to 8  $\mu\text{g/ml}$  (8). Lundergan et al. (9), developed a simplified gentamicin dosing protocol for neonates using a loading dose followed by once-daily dosing. Neonates had a gestational age  $\geq 37$  weeks and a birth weight  $\geq 2500$  grams. Initial peak serum gentamicin concentrations were higher in protocol neonates than in control neonates ( $p < 0.05$ ). Trough serum gentamicin concentrations were lower in protocol neonates than in control neonates ( $p < 0.05$ ). Trough serum gentamicin levels were < 2  $\mu\text{g/ml}$  in protocol neonates. All peaks of serum gentamicin levels in term protocol neonates were 5 to 12  $\mu\text{g/ml}$ ; compared with 84% in control neonates.

Usually, 2.5 mg/kg gentamicin is infused twice-daily. Kiatchosakun et al. (10), treated 105 neonates with a  $\geq 34$  gestational weeks and a birth weight > 2,000 grams, the dose of gentamicin was 4 mg/kg. The peak serum concentrations achieved a therapeutic level > 4  $\mu\text{g/ml}$  in 102 neonates (97%); while, 7 (6.67%) had an undesirable trough level > 2  $\mu\text{g/ml}$ . Gentamicin once-daily of 4 mg/kg in neonates  $\geq 34$  weeks of gestation achieved appropriate peak and trough levels.

Fifty-eight very-low-birth weight neonates (600 to 1,500 grams birth weight), were randomized to receive either a new dosing schedule (every 48-hours) or (once-daily) (11). Infants in the 48-hours group received gentamicin at 5.0 or 4.5 mg/kg per dose and infants in the once-daily group received 2.5 or 3.0 mg/kg. Peak serum gentamicin concentrations were significantly higher in 48-hours group infants than in the once-daily group ( $p = 0.000$ ). Ninety percent of peak serum concentrations in 48-hours group infants had a therapeutic range of 6 to 12  $\mu\text{g/ml}$  as compared with 55% in the once-daily group ( $p = 0.000$ ). None of the infants in the 48-hours group had subtherapeutic serum gentamicin concentrations as compared with 36% of the infants in the once-daily group ( $p < 0.005$ ). Trough serum gentamicin concentrations were significantly lower in infants of the 48-hour group than in infants in the once-daily group. The 48 hours dosing schedule of gentamicin given to very-low-birth weight infants during the first week after birth achieved higher therapeutic serum gentamicin peak concentrations to MIC ratios for microorganisms in all infants.

Rao et al. (12), compared the efficacy and safety of once-daily to multiple doses of gentamicin in suspected or proven septic neonates. Data suggest that the pharmacokinetic properties of once-daily is superior to multiple doses in that it achieves higher peak levels while avoiding toxic trough levels of gentamicin. Krishnan and George (13) compared the pharmacokinetic profiles of gentamicin given a once-daily dose (4 mg/kg), and a twice-daily dose (2.5 mg/kg) in 18 preterm neonates. Optimum therapeutic peak level after the first dose was achieved only with the once-daily gentamicin regimen. Alsaedi (14) compared a once-daily dosing regimen (4 mg/kg,  $n = 50$ ) to the twice-daily dosing regimen (2.5 mg/kg,  $n = 50$ ) in the first 7 days of life. The gentamicin

peak concentrations were higher in the once-daily group than in the twice-daily group ( $p= 0.001$ ). Six percent ( $n=3$ ) of infants in the once-daily group, and 26% ( $n = 12$ ) infants in the twice-daily group had trough serum gentamicin concentrations  $> 2 \mu\text{g/ml}$ . Twenty-seven neonates were given 2.0 to 2.5 mg/kg gentamicin twice-daily; while 27 neonates were given 4.0 to 5.0 mg/kg gentamicin once-daily (15). Peak gentamicin serum concentrations were lower in the twice-daily dose than in the once-daily dose ( $p<0.05$ ). The trough concentrations were higher in the twice-daily dose than in once-daily dose ( $p< 0.05$ ). Once-daily gentamicin dosing is more efficient and safer than twice-daily dosing of gentamicin.

The extending interval of gentamicin dosing has been studied by several authors. Thingvoll et al.(17) developed and valuated a 48-hour gentamicin dosing regimen for infants born  $< 28$  weeks of gestation. A total of 30 preterm infants received 4.5 mg/kg gentamicin every 48 hours and 60 infants received 2.5 mg/kg gentamicin once-daily. The mean gentamicin peak concentrations were higher in 48-hour dosing than in once-daily ( $p< 0.001$ ). The mean gentamicin trough concentration was lower in 48-hour dosing than in once-daily dosing ( $p< 0.001$ ). Gentamicin given every 48-hour is more efficient and safer than the once-daily dose. Mercado et al. (18), administered gentamicin intravenously to 20 neonates (birth weight ranged between 750 and 1,500 grams). Ten neonates received 2.5 mg/kg once-daily, and other 10 neonates received 5 mg/kg every 48-hour. Mean gentamicin peak levels were higher ( $p<0.001$ ), and gentamicin trough concentrations were lower ( $p = 0.04$ ) in the 48-hour groups than in the once-daily group. Low et al. (19) administered gentamicin to 43 preterm infants and to 70 full-term infants. The dosing regimens

were 5 mg/kg every 48-hour (birth weight  $< 1,200$  grams), 5 mg/kg every 36 hours (birth weight ranging between 1,200 and 2,500 grams), and 5 mg/kg once-daily in term infants. Of 113 neonates, 99.1% achieved target trough serum gentamicin  $< 2 \mu\text{g/ml}$  and none of the neonates had subtherapeutic peak levels  $< 5 \mu\text{g/ml}$ . Watterberg et al. (20), studied the pharmacokinetic variables in 100 neonates to evaluate the need for a loading dose. Forty-five of these neonates would not achieve gentamicin peak serum concentration  $\geq 5 \mu\text{g/ml}$  after a dose of 2.5 mg/kg once-daily. A loading dose of 4 mg/kg resulted in a gentamicin peak level  $\geq 5 \mu\text{g/ml}$ .

Hypoxic ischemic encephalopathy is a syndrome of disturbed neurologic function that occurs secondary to decreased blood oxygenation or diminished brain perfusion as a result of an asphyxia event in the perinatal period. Therapeutic hypothermia is the current standard intervention for neonates with hypoxic ischemic encephalopathy. Hypothermia is associated with decreased glomerular filtration rate, therefore impairs the elimination of renally excreted drugs. Hypothermia decreases the renal clearance, the cardiac output, and increased blood viscosity, blood redistribution and renal renin secretion. The half-life ranged between 9 and 16 hours in neonates undergoing therapeutic hypothermia ( $n = 16$ ), and 6.56 hours in neonates not undergoing hypothermia ( $p <0.001$ ). The trough gentamicin level was higher in neonates undergoing hypothermia than controls ( $p< 0.05$ ) (21). Ting et al. (22), administered gentamicin at 2.5 mg/kg every 12-hours. 85% of infants undergoing therapeutic hypothermia had a gentamicin trough concentration  $> 2 \mu\text{g/ml}$ . A median gentamicin half-life was longer in infants undergoing hypothermia than in controls ( $p< 0.05$ ). Frymoyer et al. (23), evaluated the pharmacokinetics of gentamicin in 29 full-term neonates

receiving therapeutic hypothermia. At 36-hour dosing interval, a dose of 4-5 mg/kg is predicted to achieve target gentamicin peak and trough concentrations in more than 90%. A prolonged 36-hour dosing interval will be needed to achieve target gentamicin trough concentrations in this population. A total of 644 neonates weighing < 1,250 grams at birth and having < 7 days of life without evidence of renal dysfunction received a mean gentamicin dose of 3.96 mg/kg every 48-hour (24). A total of 361 neonates (56.1%), achieved peak plasma concentrations defined successfully and 610 neonates (94.7%), achieved successful trough concentrations. Rocha et al. (26), evaluated the performance of 8 different sets of population pharmacokinetics of gentamicin in 49 infants with a gestational age of 31.4±4.1 weeks. The clearance was lower in infants with a gestational age < 34 weeks than in infants with gestational age ≥ 34 weeks ( $p < 0.05$ ).

Rocha et al. (27), studied the pharmacokinetics of gentamicin in 68 infants with a gestational age and birth weight of 24-34 weeks and 600-3,100 grams, respectively. Gentamicin clearance depended on gestational age with a cutoff at 30 weeks of gestation. The younger neonates (< 30 weeks of gestation) showed a lower gentamicin clearance than infants with a gestational age of 30 to 34 weeks of gestation ( $p < 0.05$ ). The half-life was longer in younger than in older infants ( $p < 0.05$ ). Rocha et al. (27), suggested to administrate loading doses of 3.7 and 3.5 mg/kg for the infants with a gestational age < 30 weeks and 39-34 weeks of gestational, respectively. Kildoo et al. (28), studied the pharmacokinetics of gentamicin in 15 very-low-birth weight infants. All infants received two courses, but 6 infants required three courses. Gentamicin daily-dose was 2±0.2 mg/kg for the first and second courses, and 2.5 mg/kg every 12-hours for the third course.

Gentamicin dosage was adjusted to maintain serum peak of gentamicin 4 to 8 µg/ml, and trough concentrations 0.5 to 2 µg/ml. Mean serum gentamicin peak and trough concentrations were 5.9±1.1 and 1.6±0.6 µg/ml for the first, 5.7±1.2 and 1.3±0.6 µg/ml for the second, 5.1±0.8 and 1.1±0.6 µg/ml for the third course of therapy, respectively. Mean clearance for the chronologic age groups were 6.4±1.9; 7.9±3.2; 7.9±3.2; 24.1±8.0 ml/min/1.73m<sup>2</sup>, respectively. Gentamicin clearance closely correlated with creatinine clearance ( $r = 0.99$ ;  $p < 0.001$ ). This study shows that during the first month of life infants still have decreased renal function and poor gentamicin clearance. Ali et al. (29), studied the pharmacokinetics of gentamicin in preterm infants. The extremely-low-birth weight had a gestational age and a birth weight of < 29 weeks and < 1,000 grams, respectively. The gentamicin dose and the interval between doses were 5 mg/kg and 48-hour, respectively. The very-low-birth weight infants had birth weights of 1,000-1,500 grams, the low-birth-weight infants had birth weights of 1,500-2,500 grams, and normal birth weight weighed 2,500-4,000 grams. The gentamicin dose and the interval between doses were 4 mg/kg once-daily, respectively. Infants (73%) had a peak level between 6 and 12 µg/ml, 25% of infants had a peak level > 12 µg/ml, and 12% of infants had a potential trough levels > 2 µg/ml. Neonates with extremely-low-birth-weight had significantly higher half-life ( $p < 0.05$ ) than the other neonates.

Cohen et al. (30), evaluated the effects of extracorporeal membrane oxygenation on the pharmacokinetics of gentamicin in 18 infants. The gentamicin pharmacokinetics was also studied after this therapy was discontinued. The extracorporeal membrane oxygenation increased the distribution volume, prolonged the half-life, and decreased the clearance of

gentamicin. Extracorporeal membrane oxygenation affects the gentamicin pharmacokinetics. Similar results were obtained by Southgate et al. (32), in 10 infants undergoing extracorporeal membrane oxygenation. The pharmacokinetic parameters of gentamicin were similar in venous-arterial bypass and venous-venous bypass (31). A patent ductus arteriosus may influence renal and hepatic blood flow and hence pharmacokinetics of drugs in neonates compared to infants with closed ductus arteriosus. Williams et al. (33), determined the effects of patent ductus arteriosus in 106 infants and 216 infants served as controls. Gentamicin clearance was lower in infants with patent ductus arteriosus than in control infants ( $p < 0.0108$ ). The distribution volume was higher in infants with patent ductus arteriosus than in control infants ( $p < 0.0002$ ). When the gentamicin distribution volume exceeds 0.71 l/kg, it may be of predictive value for the presence of patent ductus arteriosus. Watterberg et al. (34), compared the pharmacokinetic parameters of gentamicin in 24 preterm infants weighing  $< 1,500$  grams with patent ductus arteriosus and in 16 control infants. The distribution volume was significantly greater in infants with patent ductus arteriosus than in control infants. The total body clearance and the distribution volume were not different in the two groups of infants. Touw et al. (35), investigated the gentamicin pharmacokinetics in 12 neonates with patent ductus arteriosus, and 12 neonates with closed ductus arteriosus. The distribution volume was larger and the elimination rate constant of gentamicin was smaller in neonates with patent ductus arteriosus. Patent ductus arteriosus affects the gentamicin pharmacokinetics in neonates. Gentamicin dose of 2.4 mg/kg was administered to 22 very low-birth-weight infants weighing 700-1,470 grams every 12 or 18 hours (36). Gentamicin trough concentrations were significantly

lower in those infants greater than 1,000 grams birth weight on the 18-hour schedule. Renal function matured normally as serum creatinine progressively decreased ( $p < 0.001$ ), and creatinine clearance progressively increased ( $p < 0.001$ ). Brion et al. (37), evaluated the relationship between gentamicin pharmacokinetics and glomerular filtration rate in newborn infants to estimate the appropriate interval of gentamicin administration in neonates with renal insufficiency. The interval of gentamicin dosing should be 2 to 3 times gentamicin half-life, which can be estimated from plasma creatinine concentration (gentamicin half-life =  $2.0 + 7.7$  plasma creatinine concentration).

The interval between the doses should be adjusted according to peak and trough gentamicin levels. Lulic-Botica et al. (38), compared gentamicin pharmacokinetics among neonates born small-for-gestational age and appropriate-for-gestational age. The body weight, the gentamicin clearance, the elimination rate constant, and the clearance were lower in small-for-gestational-age whereas the gentamicin half-life was longer in the small-for-gestational age. Friedman et al. (39), investigated the effects of asphyxia in 80 asphyxiated infants receiving 2.5 mg/kg gentamicin once-daily. The gentamicin half-life was prolonged and the clearance was lower in asphyxiated infants than in controls. Gentamicin concentrations should be monitored in asphyxiated infants. Very little is known about the gentamicin resistance in neonates. Out of 130 culture proven, gram-negative cases were 71 (54%), and 59 (45.6%) were gram-positive bacteria. *Staphylococcus aureus*, was the most common bacteria in 35 infants (26.9%) followed by *Escherichia coli* in 30 infants (23.1%) cases. Gentamicin had resistance in 55.1% cases. Despite a lower peak concentration, preterm neonates were predicted to have a

higher bacterial killing effect than term neonates for the same per-kilogram dose because of gentamicin's longer half-life (41).

## 5- CONCLUSION

In conclusion, Gentamicin is a bactericidal aminoglycoside antibiotic. Gentamicin is active against the majority of aerobic gram-negative bacilli such as *Pseudomonas*, *Klebsiella* and *Escherichia coli*. Gentamicin is passively filtered unchanged by the glomerulus. In newborn infants, the rate of renal elimination increases with the neonatal maturation, and the gentamicin half-life decreases by more than 50% in the first 7-10 days after birth. The half-lives of gentamicin are 11.45, 7.9, 8.7, and 9.17 hours in extremely-low-birth weight (< 1,000 grams) in very low-birth-weight (1,000-2,500 grams), in low-birth weight (1,500-2,500 grams), and in normal-birth-weight (2,500-4,000 grams), respectively. The half-life in extremely-low-birth-weight is significantly longer than those in the other neonates.

The dose of gentamicin is 3 µg/kg once-daily for preterm neonates < 35 weeks of gestation, and 4 µg/ml once-daily for neonates > 35 weeks of gestation. The gentamicin dosage intervals vary with the postnatal neonatal age and with the serum gentamicin concentrations. At 22 hours after gentamicin administration, the dosing intervals are 24-hour, 36-hour, and 48-hour when the gentamicin concentrations are ≤ 1.2 µg/ml, 1.3 to 2.6 µg/ml, and ≥ 3.6 µg/ml, respectively. The extended interval of 48 hours and a dose of 5 µg/kg is preferred than twice-daily administration of 2.5 µg/mg gentamicin. The extended interval improves the success in achieving target peak and trough concentrations. The gentamicin peak and trough concentrations vary in wide intervals, and the gentamicin serum concentrations should be monitored when the treatment is 48 hours or more. The peak concentration should be > 5 µg/ml (at least 8 times the MIC), to be

effective and the trough concentrations should be < 2 µg/ml to avoid toxicity. In order to have high peak concentrations shortly after administration, it has been suggested to administer a loading dose of 4 mg/kg gentamicin followed by 2.5 mg/kg gentamicin once-daily. The infants of small-for-gestational age had a lower body weight and gentamicin clearance and longer half-life than the infant appropriate-for-gestational age. Hypoxic ischemic encephalopathy receiving therapeutic hypothermia, extracorporeal membrane oxygenation, patent ductus arteriosus, and perinatal asphyxia reduce the gentamicin clearance. Ototoxicity and nephrotoxicity of gentamicin are associated with a gentamicin trough concentration > 2 µg/ml.

## 6- CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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