Once daily gentamicin dosing in full term neonates

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ABSTRACT

Objective: There is no uniformity in the current recommendations of dosing regimen of gentamicin for neonates. We conducted this study to compare once-daily dosing regimen to the twice-daily dosing regimen for neonates with birth weight of ≥2500 g during the first 7 days of life.

Methods: Fifty full term infants with birth weight of ≥2500 gm admitted to the neonatal intensive care unit of King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia between November 1999 to October 2000 and received gentamicin at a dose of 2.5 mg/kg every 12 hours (control group) were compared with 50 term infants who received gentamicin at dose of 4 mg/kg every 24 hours during the period of November 2000 until October 2002 (protocol group). Trough and peak serum gentamicin levels (SDL) were measured on all infants.

Results: Peak SDL was 8.4 ± 1.8 µg/ml in the protocol group, compared to 6.7 ± 2 µg/ml in the control group (p= 0.001). Ninety-eight percent (n=49) of the protocol group, compared to 86% (n=43) of the control group, had peak SDL in therapeutic range. Fifty-eight percent (n=29) of infants in the protocol group, compared to 24% (n= 12) of infants in the control group, had peak SDL in higher therapeutic range of 8-12 µg/ml. Six percent (n=3) of the protocol infants, compared to 26% (n=13) of the control infants, had trough SDL >2 µg/ml. Six infants (12%) in the protocol group, versus 20 infants (40%) of the control group, required a dosing adjustment.

Conclusion: Gentamicin dose of 4 mg/kg given at 24-hour interval achieved significantly higher peak and safe trough serum concentrations in term infants, compared to the twice-daily regimen of 2.5 mg/kg. We suggest that measurement of gentamicin concentration may be not required when once-daily regimen is prescribed for 72 hours to term infants with suspected sepsis.

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Gentamicin in combination with penicillin or ampicillin are still frequently used for empirical treatment of early onset proven or suspected neonatal sepsis.[1-2] Gentamicin is active against aerobic *Gram-negative bacilli* as well as it has synergistic effects with penicillins. Gentamicin spectrum of antimicrobial activity, relatively low cost, and known pharmacokinetics profile make it an excellent choice for 2-3 days rule-out sepsis work-up in neonatal intensive care unit (NICU). Since the gentamicin's narrow therapeutic index and potential renal and auditory toxicity, drug monitoring is considered mandatory.[3-4] Target peak serum concentrations range from 5-12 ug/ml and trough concentration is <2 ug/ml.[5-6] For neonates several dosing strategies have been evaluated considering gestational and postnatal age as well as body weight.[3,4,7-9] The current recommendations for gentamicin dosing intervals in full term neonates vary between 12 and 24 hour.[3,4,7-9] The aim of this study is to report our experience of twice versus once daily dosing intervals of gentamicin in full term newborns who had septic work-up for suspected infection.

Methods. Newborn infants in level II and III of NICU of King Abdul-Aziz University Hospital, Jeddah,

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Kingdom of Saudi Arabia who were started on gentamicin and ampicillin for suspected or culture proven infection including bacterial sepsis, pneumonia, prolonged rupture of membrane or meconium aspiration syndrome were the subject of this study. Inclusion criteria were 1. the full term newborns (gestational age 37-42 week), 2. birth weight of ≥2500gm, 3. postnatal age ≤7 days, 4. APGAR score ≥ 5 at 5 minutes and 5. at least one trough and peak serum gentamicin levels were available. Exclusion criteria were 1. history of perinatal asphyxia or shock, 2. renal impairment and 3. maternal exposure to drugs, which may impair the newborn's renal function such as gentamicin and indomethacin within 8 hour of delivery. The following laboratory and clinical data was noted when available: blood, urine, cerebrospinal fluid cultures, differential white blood count, platelets count, serum urea, creatinine, daily urine output, and use of concurrent medications. The time was noted for all gentamicin doses and all gentamicin serum drug levels (SDL). The charts of neonates receiving gentamicin and having at least 2 serum gentamicin levels measured during the 12 months period from November 1999 to October of 2000 were retrospectively reviewed as a control group. At that time it was our practice to administer gentamicin to term neonates weighing ≥2500 gram at 2.5 mg/kg/dose intravenously every 12 hour. From November 2000, based on the available literature, gentamicin dosing was changed to 4 mg/kg every 24 hour without loading dose and the infants were followed prospectively until October 2002 as a protocol group. Gentamicin doses were infused during a 30-minute period via an infusion pump. An Initial trough SDL was routinely drawn immediately before the third dose and peak SDL were drawn 30 minutes after the end of third dose infusion. Gentamicin sulfate (Pan-gentamicin, Laboratories Panpharma, Fougeres, France) were diluted to one to 2 mg/ml and infused over a 30-minute period with metered syringe pumps and microbore tubing. Gentamicin SDL were measured by enzyme multiplied immunoassay. The aim of the therapeutic drug monitoring was to maintain gentamicin concentrations in the normal therapeutic range (peak concentration, 5-12 ug/ml; trough concentration, <2 ug/ml). The duration of the gentamicin treatment was at the discretion of the treating neonatologist.

Data from the 2 groups was compared using unpaired t-test (serum peak and trough), chi-square test (x^2) and Fisher's exact test for discrete variables such as percent of trough >2 µg/ml and percent of peaks <5 µg/ml. Results are expressed as mean ± standard deviation.

Results. Fifty infants received gentamicin at 12 hourly intervals (control group) were evaluated retrospectively and 50 infants received gentamicin at 24-hour intervals was followed prospectively (protocol group). The demographic data and gentamicin concentrations of the 2 groups are displayed in **Tables 1 and 2**. During the twice-daily gentamicin period, 7 infants (14%) had sub-therapeutic peak gentamicin serum concentration (<5µg/ml). No infant showed peak serum concentration above the upper limit of the therapeutic range (12µg/ml). Elevated trough concentrations (>2µg/ml) were found in 13 infants (26%). Twelve (24%) of infants in the control group, had peak SDL in higher therapeutic range of 8-12 µg/ml. During the once daily gentamicin period, 2 infants (4%) had sub-therapeutic peak gentamicin serum concentration. An elevated peak concentration was found in only one infant (2%). The remaining 49 (98%) infants had peak gentamicin concentrations in the desired therapeutic range (**Table 2**). Elevated trough concentrations were found in 3 infants (6%). Twenty-nine infants (58%) had peak SDL in higher therapeutic range of 8-12 µg/ml. Altogether, 12% of the infants on once daily gentamicin dosing (protocol) required at least one change in dosage regimen to achieve SDL in the desired range, compared with 40% of the infants in 12 hourly gentamicin dosing group (control) (p<0.01). Infants in the protocol group were significantly more likely to have peak and trough SDL in the desired range than infants in the control group (**Table 2**). The peak SDL in the protocol group was significantly higher than the control group (8.4 ± 1.8 µg/ml versus 6.7 ± 2 µg/ml, p<0.01). However, there was no significant difference in the trough SDL between the protocol and the control groups (1.3 ± 0.8 µg/ml versus 1.8 ± 0.9 µg/ml, p=0.4). There was no significant difference in the serum creatinine level and the urine output between the 2 groups. No treatment failure was observed applying clinical and laboratory assessment during both periods. The indication for antibiotic treatment was to rule out sepsis in 60% of the cases (**Table 3**). All patients received concurrent ampicillin, with an average dose of 100 mg/kg/day. The combination of antimicrobials was tailored in each patient based on clinical judgment or culture results, or both.

Discussion. In this study, we found that term infants given a once-daily dose of 4 mg/kg gentamicin, 1. had significantly higher mean peak SDL, 2. had a similar mean trough SDL, 3. were more likely to have all SDL in the target range and subsequently, less needs for dosing adjustment compared with term infants in the twice daily gentamicin regimen of 2.5 mg/kg and 4. the adjustment in the dosage in the twice-daily regimen was required mainly due to toxic trough SDL (26% of cases). Several gentamicin-dosing regimens have been recommended in an attempt to achieve optimal therapeutic serum concentration. There has been recent interest in once daily dosing of aminoglycosides as larger doses given at longer intervals are likely to improve efficacy and reduce toxic effects. Bacterial killing by aminoglycosides, such as gentamicin, is concentration dependent. Aminoglycoside efficacy is correlated with the ratio of peak serum concentration of drug to the minimum inhibitory concentration (MIC) of

Table 1 - Patient characteristics at study entry.

Patient characteristics	Twice-daily dosing group	Once-daily dosing group
Gestational age (week)		
Mean ± SD	38.9 ± 1.8	38.9 ± 1.7
Range	37 - 41	37 - 40
Postnatal age (days)		
Mean ± SD	0.6 ± 1.1	0.5 ± 1.0
Range	0.5 - 1.7	0.5 - 1.5
Birth weight (grams)		
Mean ± SD	3200 ± 700	3300 ± 6 00
Range	2500 - 5500	2500 - 4400

Table 2 - Serum gentamicin concentrations.

Infants different SDL	Twice-daily dosing group	Once-daily dosing group
N of infants (M/F)	50 (35/15)	50 (35/15)
Peak (µg/mL)		
Mean ± SD	6.7 ± 2.0	8.4 ± 1.8*
Range	1.3 - 11	4.8 - 13
N of SDL <5 µg/mL (%)	7 (14)	2 (4)
N of SDL 8-12 µg/mL (%)	12 (24)	29 (58)†
N of SDL>12µg/mL (%)	0 (0)	1 (2)
Trough (µg/mL)		
Mean ± SD	1.5 ± 0.9	1.3 ± 0.8
Range	<0.5 - 3.4	<0.5 - 1.9
N of SDL>2µg/mL (%)	13 (26)	3 (6)†
N of SDL in therapeutic range (%)‡	30 (60)	44 (88)†

*p< 0.05 by unpaired t test, †p< 0.05 by x^2 analysis,
‡Trough <2 and peak 5 - 12 µg/mL, SDL - serum drug level,
M - male, F - female

Table 3 - Patient diagnosis at study entry.

Diagnosis	Twice-daily dosing group (N of patients)	Once-daily dosing group (N of patients)
Rule- out sepsis	30	29
Pneumonia	6	8
Meconium aspiration	3	4
Jaundice	7	5
PROM	3	3
Seizure	1	1

PROM - prolonged ruptured of membrane

the treated organism.[10,11] The clinical outcome was better and the mortality rate was lower in adult patients with pneumonia and sepsis caused by gram-negative bacteria when peak serum aminoglycoside concentrations exceeded 5µg/ml during the first 72 hours of treatment.[11,12] None of our infants suffered from gram-negative sepsis. The use of once-daily dosing regimens in aminoglycoside therapy results in intervals when drug concentrations are below the MIC. This might foster concern that target pathogens would proliferate once concentrations of drug fall below the MIC; however, aminoglycoside have a potent post antibiotic effect (PAE); that is, suppression of bacterial growth persists despite concentrations of antibiotic below the MIC.[13-15] The PAE is extended by higher doses of aminoglycosides.[16] Adaptive resistance refers to the reduction in the rate of bacterial killing by an antibiotic following preexposure to that drug. Adaptive resistance to an aminoglycosides is transient and reversible.[17,18] The transient nature of adaptive resistance means that the organisms exposed to once-daily doses of gentamicin can revert to sensitive phenotype during the interval when the antibiotic concentrations are low.[18] Our results are similar to what had been reported by Skopnik and Heimann[8] and Hayani et al.[7] Skopnik and Heimann[8] in a retrospective study compared peak and trough SDL of 223 term infants who received gentamicin dose of 2-2.5 mg/kg every 12 hour with 79 term infants received gentamicin dose of 3.5-4 mg/kg every 24 hour. They found that the mean peak gentamicin SDL was significantly higher in the once daily regimen, whereas the mean trough SDL was in the comparable range in both groups. Hayani et al[7] studied gentamicin pharmacokinetics in term newborns. They randomized 11 term infants to receive 5 mg/kg every 24 hour and 16 infants to receive 2.5 mg/kg every 12 hour. The gentamicin was given either intramuscularly or intravenously. They found a significantly higher mean peak SDL in the 24-hour intervals group but similar mean trough SDL in the 2 groups. Thureen et al[9] showed that gentamicin dosage of 4mg/kg given at 24-hour intervals achieved significantly higher peak and lower trough SDL compared to the group receiving gentamicin dosage of 2.5 mg/kg given at 12-hour intervals. However, 50% of the infants in their study receiving 12-hourly dose were 34-37 week gestation whereas only 26% of those receiving 24 hourly doses were preterm, suggesting a bias toward administering 12 hourly doses to preterm infants. Lundergan et al,[19] using a bolus gentamicin dose of 5 mg/kg followed by 4 mg/kg every 24 hour in term infants ≥2500g, also showed significantly higher peak and lower trough SDL compared to historical controls who were given 2.5 mg/kg every 12 hour. Recently, Garwal et al[20] randomized 20 term infants to receive gentamicin at a dose of 4 mg/kg every 24 hour and 21 infants to receive gentamicin at a dose of 2.5 mg/kg every 12 hour. They found that the gentamicin mean peak SDL was significantly higher and the mean trough SDL was lower

in the 24 hour-intervals group compared with the 12 hour-interval group. There is evidence that less frequent administration of aminoglycosides such as once daily administration might lower the risk of nephro- and ototoxicity while preserving or even enhancing antibacterial efficiency.[12] This is partially explained by saturable uptake kinetics of aminoglycoside in the inner ear and kidney as well as by the concentration dependent bacteriocidal activity of aminoglycosides and prolongation of their post antibiotic effect with increases in peak concentration.[21] In some full term neonates adherence to a twice-daily schedule might cause sub-therapeutic peak concentrations during the initial phase of therapy, even if peak concentration in the low normal therapeutic range (≤6 µg/ml) is reached later on under steady state conditions.[22] Furthermore, during twice-daily aminoglycoside period potentially toxic trough concentrations occurred frequently as has been reported by others.[3,4,9] Therefore, monitoring of serum aminoglycoside concentration is mandatory when a twice-daily aminoglycoside regimen is employed in full term neonates.[3,4] In our study, a dosage adjustment was necessary in 40% of cases in the twice daily regimen. The experience with once daily regimen is promising. In only 12% of cases was a dosage adjustment required. By increasing the dosing interval to 24 hours in full term neonates undesired sub-therapeutic peak were found in only 2 (4%) infants. We suggest that measurement of gentamicin concentration may be not required when once-daily regimen is prescribed for 72 hour to term infants with suspected sepsis.

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