Once-Daily Gentamicin Dosing of 4 Mg/Kg/Dose in Neonates

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Since gentamicin is one of the most commonly prescribed antibiotics for culture-proven or suspected sepsis in neonates, interest has increased in refining dosing regimens for improved efficacy and decreased toxicity. Usually, 2.5 mg gentamicin/kg is infused twice daily, but its large volume of distribution, slow renal clearance and concentration-dependent character, suggests longer dosing intervals would be more appropriate. From a previous study, 22% of neonates who received a once-daily gentamicin dosage of 5 mg/kg/day had unacceptably high trough levels (i.e. > 2 μg/mL). The authors studied 105 neonates (of ≥ 34 wk gestational age or ≥ 2,000 g body weight) admitted to the Neonatal Unit, Srinagarind Hospital, Khon Kaen University; at risk, or with clinical features of sepsis, receiving a once-daily gentamicin dosing of 4 mg/kg intravenously. 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 treated with 4 mg gentamicin/kg once-daily had a mean steady-state peak vs trough concentration of 7.33 (± 2.77) vs 0.99 (± 0.57) μg/mL, respectively. The peak serum concentration achieved a therapeutic level > 4 μg/mL in 102 neonates (97%), while 7 (6.67%) had an undesirable trough level (viz. > 2 μg/mL); notwithstanding, no nephrotoxic or ototoxic effects were identified. Gentamicin once-daily at 4 mg/kg/dose in neonates at ≥ 34 wk gestation achieved appropriate trough levels: the regimen was convenient and did not increase renal or ototoxicity.

Keywords: *Once-daily, Gentamicin, Neonate*

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The combination of ampicillin and gentamicin is the most common empirical antibiotic therapy for early-onset, suspected or proven neonatal sepsis because of its broad antimicrobial spectrum and relatively low cost. Gentamicin dosing schedules for term and large premature neonates during the first week of life range between the standard dosage of 2.5 mg/kg every 12 hours and 4-5 mg/kg every 24 hours[1-4]. The target peak serum concentration ranges between 4 and 12 mg/mL with a trough concentration < 2 mg/mL[5-7]. Although gentamicin concentration-monitoring is recommended, it is not practicable in Thailand due to the need for extra serum sampling, limited laboratory capacity in remote areas, and the additional cost.

An extended interval of once-daily gentamicin dosing in adults has been used for the past 15 years[5], based on efficacy principles, viz.: 1) concentration-dependent bacterial killing; 2) post-antibiotic effect; and, 3) adaptive resistance[8]. Indeed, gentamicin is eliminated via glomerular filtration, but a fraction is reabsorbed in the proximal tubule. Renal uptake of gentamicin exhibits a saturation phenomenon, wherein the accumulation is less when administered in one large dose than by continuous infusion[9].

The reported incidence of gentamicin induced nephrotoxicity is usually assessed by a rise in serum creatinine concentration of over 0.5 mg/dL[5-10]. Toxicity is correlated with an elevated drug trough

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concentration (i.e. > 2 μg/mL) and prolonged therapy (i.e. > 10 days), but not with higher peak concentrations[5]. Extending dosing intervals yields a longer period at a lower drug concentration, thereby producing less renal toxicity. Renal function is strongly linked to gestational and postmenstrual age. The association between gentamicin and ototoxicity in adults is well-documented[5-10], however, reports of neonatal ototoxicity to gentamicin are uncommon and usually associated with concomitant administration of other ototoxic medications such as furosemide and/or vancomicin[5].

Studies comparing conventional dosing with once-daily aminoglycoside regimens in adults found that the latter provide high peak and low trough serum concentrations with equal efficacy and toxicity[11,12]. In a previous study by the authors, 22% of neonates receiving the once-daily dose of 5 mg gentamicin/kg/day produced undesirable trough levels (i.e. > 2 μg/mL)[23].

The authors conducted a study to determine the serum peak and trough levels of gentamicin in neonates on a once-daily dosing of 4 mg/kg, and to develop a standard gentamicin dosage regimen that would result in fewer troughs > 2 μg/mL.

Material and Method

The study was conducted at Srinagarind Hospital, Khon Kaen University, between June 2002 and March 2003. The study protocol was approved by the Institutional Review Board. The authors included neonates: 1) of ≥ 34 wk gestational age or ≥ 2,000 g body weight at risk, or with clinical features of, sepsis; 2) of postnatal age < 7 days; 3) receiving gentamicin therapy ≥ 48 hours; and, 4) for whom informed parental consent was given. The exclusion criteria were: an Apgar score < 4 at 1 and/or 5 minute(s), cardiopulmonary arrest, shock, seizures, congenital malformation incompatible with life, anomalies of the kidney or renal failure from other causes. The duration of gentamicin therapy was determined by the attending physician.

The demographic patient information collected included gestational age (GA) and birthweight (BW). GA was determined from the maternal history, ultrasound examination (if available), and their Ballard score. Perinatal and maternal histories were obtained to identify risk factors for both sepsis and serum drug levels outside of the desired range (i.e. antenatal exposure to gentamicin within 8 hours of delivery). The Apgar score was recorded at 1 and 5 minutes. A blood sample was collected for baseline blood culture, complete blood count, blood urea nitrogen (BUN), and creatinine levels.

Gentamicin was administered as a slow infusion 4 mg/kg every 24 hours over a 30-minute period using a syringe pump, through microbore tubing, followed by administration of a routine flushing solution. The trough serum gentamicin concentration was collected within 30 minutes (i.e. before the third dose) and its peak 30 minutes after the infusion. Gentamicin serum concentrations were determined using a fluorescence-polarization immunoassay (Abbott TDX/FLX; Abbott Park; Illinois). Repeated blood urea nitrogen and creatinine levels were obtained on day 3 to assess nephrotoxicity. Ototoxicity was evaluated by a hearing test using audiometry before discharge and scheduled for brainstem auditory evoked potentials six months later.

Results

One hundred and five neonates met the inclusion criteria for starting on gentamicin therapy and were evaluated prospectively. The demographic data are presented in Table 1. The majority (98%) received concurrent ampicillin 100-200 mg/kg/day. The remaining patients received an additional antimicrobial agent (viz. penicillin, cloxacillin, cefotaxime or acyclovir). The combination of antimicrobial therapy was tailored for each patient based on clinical judgment and/or culture results.

One hundred and five neonates were evaluated and treated with a once-daily 4 mg/kg gentamicin regimen. The mean steady-state peak and trough serum gentamicin concentrations were 7.33 (± 2.77) and 0.99 (± 0.57) μg/mL (Tables 2 and 3), respectively. 102 neonates (97%) had a peak serum therapeutic concentration > 4 μg/mL and 3 had a peak

Table 1. Baseline Characteristics (n = 105)

Male	53
Female	52
Gestational age, weeks (mean ± SD)	39±1.4
BW, grams (mean ± SD)	3264±565
Age, hours (mean ± SD)	14±22
Maternal conditions	
PROM > 24 hours	12
Fever	3
Urinary tract infection	4
Maternal antibiotics	8
Gentamicin	4
Thick Meconium stained amniotic fluid	20
Mild to moderate asphyxia	19

Table 2. Peak gentamicin level at 4 mg/kg/dose (n = 105)

Mean (μg/mL) ± SD	7.33±2.77
Range (μg/mL)	2.10-22.35
Peak > 4.0 mg/mL (%)	102 (97.00)
Peak > 12.0 mg/mL (%)	3 (2.85)

Table 3. Trough gentamicin level at 4 mg/kg/dose (n = 105)

Mean (μg/mL) ± SD	0.99±0.57
Range (μg/mL)	0.17-3.26
Trough < 2.0 μg/mL (%)	98 (93.33)

> 12 μg/mL (viz. 12.74, 21.00 and 22.35 μg/mL). Seven neonates (6.67%) had an undesirable trough level that was slightly over 2 μg/mL (viz. 2.06, 2.07, 2.12, 2.33, 2.45, 2.67 and 3.26 μg/mL); however, no nephro- or oto-toxic effects were identified. The mean serum creatinine levels at baseline and on day 3 after treatment were 0.9 ± 0.2 mg/dL and 0.5 ± 0.2 mg/dL respectively, no oliguric or polyuric problems occurred during therapy. The results of the hearing screen before discharge in 100 neonates were normal. Five neonates on whom the hearing test was not done before discharge were lost to follow-up, however, they received only 3 days of gentamicin therapy with normal trough levels. Forty-seven neonates of whom brainstem auditory evoked potentials were done had normal hearing. All seven neonates whose trough level over 2 g/mL had normal both audiometry and brainstem auditory evoked potentials.

A good clinical outcome was observed. Four infants with a history of antenatal exposure to gentamicin had desirable drug levels.

Discussion

Gentamicin, in combination with ampicillin or penicillin, is the standard antibiotic therapy for suspected or early-onset neonatal sepsis[1-4]. A potential drawback to gentamicin therapy is the need to monitor the serum drug level to ensure achievement of concentrations which are effective and minimize the likelihood of renal- and oto-toxicity.

Recent studies suggest that administration of higher dosages and longer intervals may improve efficacy and reduce the toxicity associated with gentamicin therapy[13-15]. Because gentamicin exhibits concentration-dependent killing activity, a higher peak serum concentration to a minimal inhibitory concentration ratio improves bacterial killing[16].

So, a longer dosing interval and lower trough concentration may prevent adaptive microbial resistance while reducing toxicity[15,17]. Indeed, once-daily administration of gentamicin has been shown safe and efficacious in neonates > 34 weeks and less costly than a twice-daily regimen[17-23].

In a pharmacokinetic study of gentamicin 5 mg/kg once-daily vs 2.5 mg/kg twice-daily in infants > 34 wk gestation at Srinagarind Hospital, peak serum concentrations were significantly higher and trough serum concentrations significantly lower in the 5 mg/kg once daily group. However, 22% of neonates in the 5 mg/kg once-daily group had trough serum gentamicin concentration values > 2 μg/mL[23].

The present study confirmed that neonates receiving 4 mg/kg once daily had a peak therapeutic serum concentration > 4 mg/mL in 102 neonates (97%). Seven neonates (6.67%) had an undesirable trough level over 2 mg/mL; however, no nephro- or oto-toxic effects were observed. Gentamicin appears less nephro- and oto-toxic in neonates than in older patients[7] and the role of serum concentration monitoring should be limited to specific neonatal patients.

Conclusion

Once-daily gentamicin therapy of 4 mg/kg in neonates of ≥ 34 weeks gestation results in appropriate peak concentrations, lower troughs, and lower frequency of troughs > 2 μg/mL. Routine collection of serum gentamicin concentration may not be necessary in neonates with normal renal function receiving 3 days of once-daily gentamicin of 4 mg/kg for suspected sepsis. Once-daily gentamicin dosing is preferable to any other dosing interval because it is a simple regimen that achieves desirable drug levels. Cost savings for hospitals can be realized through a reduction in laboratory labour and materials needed for serum gentamicin concentration analysis.

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การให้ยา Gentamicin ขนาด 4 มก./กก./วัน วันละครั้งในทารกแรกเกิด

ผกาพรรณ เกียรติชูสกุล, ภพ โกศลารักษ์, จรรยา จิระประดิษฐา, สุกัญญา ทักษพันธุ์, สมพนธ์ ทัศนิยม

เนื่องจาก gentamicin เป็นยาปฏิชีวนะ ที่ใช้บ่อยในทารกแรกเกิดซึ่งมีหรือสงสัยว่ามีการติดเชื้อในกระแสเลือด เป็นยาที่มีราคาถูกและประสิทธิภาพดี การให้ยา gentamicin ในทารกแรกเกิด ในอดีตมักให้ในขนาด 2.5 มก./กก./ครั้ง วันละสองครั้ง แต่ระยะหลังมีความพยายามที่จะหาขนาดและระยะห่างของการให้ยาที่เหมาะสมในทารกแรกเกิด เพื่อเพิ่มประสิทธิภาพในการรักษาและลดผลข้างเคียงของยา เนื่องจาก gentamicin มีปริมาตรการกระจายตัวของยาสูง และมีการกำจัด ยาออกทางไตในทารกแรกเกิดได้ช้า นอกจากนั้นฤทธิ์การกำจัดเชื้อของยายังขึ้นกับระดับความเข้มข้นสูงสุดของยาในเลือด การให้ยาวันละครั้งเพื่อทำให้ระดับยาสูงสุดในเลือดสูงและระดับยาต่ำสุดในเลือดมีค่าต่ำ น่าจะเป็นวิธีที่เหมาะสมในทารกแรกเกิด อย่างไรก็ตามจากการศึกษาที่ผ่านมาของกลุ่มผู้วิจัยพบว่าร้อยละ 22 ของทารกแรกเกิดที่ได้รับยา gentamicin ขนาด 5 มก./กก./วัน วันละครั้ง ทำให้ระดับยาต่ำสุดในเลือดของทารกสูงกว่าค่าที่ยอมรับได้คือสูงกว่า 2 มคก./ มล.ดังนั้น gentamicin ขนาด 5 มก./กก./วัน น่าจะเป็นขนาดที่สูงเกินไปสำหรับทารกไทย การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาระดับยาสูงสุด และต่ำสุดของยา gentamicin ในทารกแรกเกิดจำนวน 105 ราย ที่มีอายุครรภ์เท่ากับหรือมากกว่า 34 สัปดาห์ หรือน้ำหนักตัว เท่ากับหรือมากกว่า 2,000 กรัม ที่เข้ารับการรักษาในหอผู้ป่วยทารกแรกเกิดโรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่นและได้รับยา gentamicin เข้าทางหลอดเลือดดำขนาด 4 มก./กก./วัน วันละครั้ง ทารกจะได้รับการตรวจหาระดับยาสูงสุดและต่ำสุดของยา gentamicin ในเลือด ในวันที่ 3 หลังจากได้รับยา และได้รับการตรวจหา BUN, creatinineในเลือด ในวันที่ 1 และ 3 เพื่อดูการทำงานของไต รวมทั้งได้รับการตรวจ การได้ยินเพื่อดูผลข้างเคียงต่อหูก่อนจำหน่ายออกจากโรงพยาบาล ผลการศึกษาพบว่า ทารกที่ได้รับยา gentamicin ขนาด 4 มก./กก./วัน วันละครั้งมีระดับยา สูงสุดในเลือด 7.33 $\pm$ 2.77 มคก./มล. และ ระดับยาต่ำสุดในเลือด 0.99 $\pm$ 0.57 มคก./ มล. ทารก 102 ราย (ร้อยละ 97) มีระดับยาสูงสุดในเลือดอยู่ในเกณฑ์การรักษา ทารก 7 ราย (ร้อยละ 6.67) มีระดับยาต่ำสุดในเลือดสูงกว่าค่าที่พึงประสงค์คือสูงกว่า 2 มคก./ มล. อย่างไรก็ตามไม่พบผลข้างเคียงต่อไต หรือผลต่อการได้ยิน ดังนั้นการให้ยา gentamicin วันละครั้งในขนาด 4 มก./กก./วัน ในทารกแรกเกิดอายุครรภ์เท่ากับ หรือมากกว่า 34 สัปดาห์ ให้ระดับยาต่ำสุดในเลือดอยู่ในเกณฑ์ที่เหมาะสม และการบริหารยาแบบวันละครั้งนี้มีความสะดวก ประหยัดค่าใช้จ่ายกว่าการให้ยาแบบดั้งเดิม รวมทั้งไม่พบผลข้างเคียงต่อไตหรือหู