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Extended-Interval Dosing of Gentamicin Aiming for a Drug-Free Period in Neonates: A Prospective Cohort Study

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Background: Current gentamicin dosing algorithms in adult populations target a high peak concentration (C_{\max}) assuring efficacy and a drug-free period (concentration <0.5 mg/L) preventing toxicity. In contrast, gentamicin-based regimens in neonatal sepsis often aim for lower peak levels and trough concentrations of 0.5 – 2.0 mg·L⁻¹. The latter concentrations are associated with an increased risk of aminoglycoside-related toxicity. Therefore, the primary aim of this study was to assess the target attainment of a simple and practical dosing regimen designed to attain drug-free periods in newborns.

Methods: The study was of prospective observational design. Neonates admitted to a level II neonatal nursery diagnosed with (suspected) early-onset sepsis and commencing intravenous gentamicin therapy of 5 mg·kg⁻¹ every 36 hours were eligible for inclusion. Gentamicin dosing was guided by drug concentration monitoring targeting C_{\max} values >8 mg·L⁻¹ and estimated trough concentrations <0.5 mg·L⁻¹. Relationships between body weight (BW), gestational age (GA), postnatal age, and pharmacokinetic parameters were analyzed using the Pearson correlation test, and univariate and multivariate logistic regression analyses were performed to identify covariates predictive of target attainment failure.

Results: A total of 184 patients were included. 90.4% of patients ($n = 166$) achieved a C_{\max} value >8 mg·L⁻¹ with a C_{\min} value <0.5 mg·L⁻¹. Subsequently, significant correlations were found between GA and C_{\max} ($r = 0.58$, $P < 0.001$) between GA and C_{\min} ($r = 0.44$, $P < 0.001$), between BW and C_{\max} ($r = 0.50$, $P < 0.001$), and between BW and C_{\min} ($r = 0.42$, $P < 0.001$). Correlations between area under the curve (AUC) and GA ($r = 0.064$, $P = 0.4$), and between AUC and BW ($r = 0.028$, $P = 0.7$) were not significant. During multivariate analysis, only GA ($P < 0.001$) was retained as an independent predictor of underexposure.

Conclusions: Extended interval dosing of gentamicin resulted in high target attainment rates in neonates admitted to a level II unit. In

line with previous reports, low GA and BW were predictive of subtherapeutic peak and toxic trough levels. The AUC, however, was unaffected by the interpatient variation in GA and BW. Since AUC-guided dosing is gaining interest worldwide, the latter finding deserves further exploration in other neonatal cohorts.

Key Words: gentamicin, aminoglycosides, pharmacokinetics, dosing schedule, neonates

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INTRODUCTION

Early-onset neonatal sepsis is one of the primary causes of mortality among neonates. It occurs in the first 7 days of life predominantly because of contaminated amniotic fluid or blood with predominant pathogens such as group B streptococcal, *Escherichia coli*, enterococci, or other gram-negative bacilli.^{1,2} Current guidelines for empirical therapy in neonates with (suspected) sepsis recommend gentamicin-based regimens in preference to cefotaxime-based treatments, because of higher susceptibility and prevention resistance due to selective pressure.³ Although the combination of the aminoglycoside gentamicin and a penicillin antibiotic has proven to be an effective treatment for staphylococcal species, enterococci, and group B streptococcal infections, it should be used with care because of the risk of aminoglycoside-related nephrotoxicity and ototoxicity.^{4,5}

Newborns have aberrant pharmacokinetics with high interpatient variability compared with adult patients. As their kidneys are still in development, aminoglycoside clearance and glomerular filtration rate are affected by gestational age (GA) and postnatal age (PNA).⁶ Furthermore, over 70% of their body weight (BW) consists of water, which results in a relatively high volume of distribution (in liters per kilogram) of hydrophilic aminoglycosides.⁷ Unfortunately, adequate diagnostic instruments are currently unavailable to sensitively and specifically identify drug-related ototoxicity and nephrotoxicity in neonates. Thereof, gentamicin trough concentrations or area under the curves (AUCs) can be considered the best clinical “markers” for toxicity monitoring.⁵

Current guidelines target a peak serum concentration (C_{\max}) range from 5 to 12 mg·L⁻¹ and trough concentration (C_{\min}) range from 0.5 to 2 mg·L⁻¹ in neonates. In adults, however, it is common to aim for a C_{\max} of 20 mg·L⁻¹ followed by a drug-free period (concentration <0.5 mg/L) of at least 4 hours.⁸ Mechanistic modeling and clinical studies

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have shown that an aminoglycoside-free period may be a key to prevent nephrotoxicity by allowing the kidney to void the accumulated drug.⁵ A recent model-based simulation by Valitalo et al⁶ showed that these targets can be successfully attained in neonates, primarily increasing the $\text{mg}\cdot\text{kg}^{-1}$ dose and extending the interval depending on PNA and BW. Another approach suggested in literature is area under the concentration–time curve (AUC)-guided dosing. The AUC is believed to be a strong predictor of (nephro)toxicity,⁹ and the AUC over minimal inhibitory concentration (MIC) ratio is the surrogate pharmacodynamic index that correlates best with resistance suppression and treatment success.¹⁰ Albeit there are limited clinical data on the optimal gentamicin exposure in terms of AUC, it has been suggested that aiming for a 90% probability of treatment success and less than 10% probability of toxicity, an $\text{AUC}_{24\text{ h}}$ value of $75\text{ mg}\cdot\text{h}\cdot\text{L}^{-1}$ should be aimed for when pathogens' MIC's are between 0.5 and $1.0\text{ mg}\cdot\text{L}^{-1}$.⁹

The majority of current dosing regimens of aminoglycosides in neonates are based on data obtained from neonates admitted to a level III intensive care unit also known as a neonatal intensive care unit (NICU). As these critically ill sometime very premature newborns show a large interpatient variability in pharmacokinetic (PK) parameters, the dosing regimens consist of complex algorithms with different dosages and intervals depending on GA, PNA, and/or BW.⁵ It is, however, debatable whether complex algorithms with known high risk of prescription errors¹¹ are required to attain predefined targets in noncritically ill neonates admitted to a level II special care unit. The interpatient and inpatient variability in PK parameters is expected to be lower in this population in comparison with neonates admitted to a NICU because of a generally better clinical condition of the former. Therefore, the 2 primary aims of this study were¹ to prospectively assess the target attainment of a simple and practical dosing regimen of $5\text{ mg}\cdot\text{kg}^{-1}$ every 36 hours aiming for a drug-free period and² to evaluate interpatient PK variability in neonates admitted to a level II neonatal special care unit.

METHODS

Study Design and Patients

In this prospective observational study, neonates admitted to the level II neonatal nursery at the Juliana Children's Hospital (The Hague, the Netherlands) diagnosed with (suspected) early-onset sepsis and commencing intravenous gentamicin therapy between January 2010 and January 2013 were eligible for inclusion. Main exclusion criteria were GA <32 weeks and PNA >7 days. The local medical ethics committee provided a waiver for consent.

Gentamicin Dosing and Monitoring

Gentamicin was dosed $5\text{ mg}\cdot\text{kg}^{-1}$ every 36 hours based on a previously published analysis by our group.¹² Gentamicin was administered as a 30-minute infusion in combination with twice daily intravenous $100\text{ mg}\cdot\text{kg}^{-1}$ amoxicillin. According to the monitoring protocol, a peak concentration and second concentration were drawn 0.5 hours

and 6–18 hours after the end of the first infusion, respectively. Gentamicin dosing was guided by drug concentration monitoring targeting C_{max} values $>8\text{ mg}\cdot\text{L}^{-1}$ and estimated trough concentrations $<0.5\text{ mg}\cdot\text{L}^{-1}$. Recommended dose adjustments were communicated by a clinical pharmacist before administration of the second dose. In case of estimated trough concentrations $>0.5\text{ mg}\cdot\text{L}^{-1}$, the dosing interval was extended. In all other cases subsequent doses were administered every 36 hours. Subsequently, drug concentrations were monitored at least once every other dose according to protocol. Antibiotic treatment was stopped if blood cultures showed no bacterial growth within 3 days. Concentrations of gentamicin were measured using an automated chemiluminescent immunoassay (Architect c8000, Abbott Laboratories, Amstelveen, the Netherlands). The coefficients of variation for the gentamicin assay of the low, median, and high controls were 4.2%, 2.1%, and 1.4%, respectively. The limit of quantification was $0.3\text{ mg}\cdot\text{L}^{-1}$.

Data Collection and Exposure Analysis

The following demographic and clinical parameters were collected and registered in patients' clinical records: date of birth, gender, BW, GA, PNA, Apgar score, date, time and dose of gentamicin administration, and blood culture results. Furthermore, individual C_{max} , $C_{24\text{ h}}$, C_{min} , area under the concentration–time curve (AUC), clearance (Cl), and volume of distribution (Vd) values were estimated using a one-compartment open model and PK software (MW/PHARM version 3.60; Mediware, the Netherlands) with an iterative 2-stage Bayesian fitting procedure. The performance of the dosing table was assessed by the calculation of percentage of patients attaining the predefined target exposure.

Statistical Analysis

Relationships between BW, GA, PNA, and PK parameters were analyzed using the Pearson correlation test. Furthermore, univariate and multivariate logistic regression analyses were performed to identify covariates predictive of C_{max} target attainment failure. A stepwise backward elimination procedure was carried out, retaining covariates only if their removal significantly changed the model ($P < 0.005$). To account for multiple testing, only those covariates were tested that significantly affected the risk of target attainment failure in univariate analysis, and a stringent P -value of 0.005 during multivariate analysis was selected. All tests were performed in SPSS Statistics version 20 (SPSS Inc., Chicago, IL), and a P -value of <0.05 was considered to be statistically significant.

RESULTS

During the 3-year enrollment period, 214 patients were diagnosed with (suspected) early-onset sepsis and treated with gentamicin treatment episodes. After exclusion of 30 patients because of insufficient data ($n = 11$), GA <32 weeks ($n = 7$), and PNA >7 days ($n = 12$), a total of 184 patients (53% were males) were included for analysis. Their GA and PNA ranged from 32 to 42 weeks and 0–6 days with a median of 39 weeks and 0 days, respectively. Their mean BW was 3.2 kg ranging

from 1.2 to 5.1 kg. Median Apgar score 10 minutes postpartum was 9, ranging from 3 to 10.

As shown in Table 1, 90.4% of patients ($n = 166$) achieved both a C_{\max} value $>8 \text{ mg}\cdot\text{L}^{-1}$ and a C_{\min} value $<0.5 \text{ mg}\cdot\text{L}^{-1}$. Because of the high attainment rate with respect to the C_{\min} target, it was decided to estimate $C_{24 \text{ h}}$ values and assess the target attainment as previously described for the eC_{\min} values at 36 hours. Just over half of the population (51.6%) attained a $C_{\min} <0.5 \text{ mg}\cdot\text{L}^{-1}$ at 24 hours. In 5 of these cases, the physician decided to shorten the dosing interval to 24 hours because of signs of severe sepsis. Furthermore, interpatient variability in Cl, half life, and Vd were 30%, 19.3%, and 16.7%, respectively. Subsequently, significant correlations were found between GA and C_{\max} ($r = 0.58$, $P < 0.001$), between GA and C_{\min} ($r = 0.44$, $P < 0.001$), between BW and C_{\max} ($r = 0.50$, $P < 0.001$), and between BW and C_{\min} ($r = 0.42$, $P < 0.001$). Correlations between AUC and GA ($r = 0.064$, $P = 0.4$) and between AUC and BW ($r = 0.028$, $P = 0.7$) were not significant (Fig. 1). In the group of 12 neonates with a PNA >7 days, a post hoc analysis was performed, which indicated that 10 of 12 patients (82%) attained predefined C_{\max} and C_{\min} targets.

Finally, univariate binary logistic regression showed that both low BW ($P < 0.001$) and low GA ($P < 0.001$) were significant predictors of C_{\max} target attainment failure. During multivariate analysis, only GA ($P < 0.001$) was retained as an independent predictor of underexposure, meaning that neonates in the lower GA range would require relatively higher dose per kilogram BW to achieve a C_{\max} value $>8 \text{ mg}\cdot\text{L}^{-1}$. Patients ($n = 16$) who did not reach C_{\max} values $>8 \text{ mg}\cdot\text{L}^{-1}$ had a C_{\max} between 4.9 and $7.9 \text{ mg}\cdot\text{L}^{-1}$. BWs in 11 of these

patients were $<2.7 \text{ kg}$ (first quartile) and 12 had a GA <35 weeks (first quartile).

Blood culture results were positive in 5 of 186 patients (2.7%), *Coagulase-negative staphylococcus* ($n = 4$) or *Corynebacterium* species ($n = 1$), 3 of which were considered to be positive because of contamination. During admittance to the special care unit routine hearing screening and kidney function monitoring in all subjects showed no signs of aminoglycoside-related ototoxicity or renal impairment.

DISCUSSION AND CONCLUSIONS

In this prospective clinical study, over 90% of the included patients reached the combined predefined C_{\max} and C_{\min} targets using a simple uniform dose of $5 \text{ mg}\cdot\text{kg}^{-1}$ gentamicin every 36 hours aiming for low C_{\min} values ($<0.5 \text{ mg}/\text{L}$) in all neonates admitted to our level II unit with (suspected) early-onset sepsis. The good performance of the gentamicin dosing regimen can be explained by a low interpatient variability in PK parameters relatively to other reports of gentamicin PK in neonates.^{5,12,13} It should be noted that most of the latter reports included neonates admitted to a level III unit. NICU populations have a high interpatient variability in both Cl and Vd because of severe (underlying) pathology and to a wider range in GA and PNA which in turn are associated with a larger range of BW and developmental stage compared with neonates admitted to a level II unit.⁵ In line with previous reports, low GA and BW were predictive of subtherapeutic peak and toxic trough levels. The AUC, however, was unaffected by the interpatient variation in GA and BW. Since AUC-guided dosing is gaining interest worldwide, the latter finding deserves further exploration in other neonatal cohorts. As neonates with a GA >32 weeks and diagnosed with (suspected) early-onset sepsis (PNA <7 days) were included in this study, patients suffering from (suspected) late-onset neonatal sepsis were not included as well as preterm neonates with a low GA (<32 weeks). The main exclusion criteria could therefore be considered as the most important limitations of the study outcomes. However, only 7 neonates were excluded because of a GA <32 weeks and no more than 12 patients had a PNA >7 days at start of gentamicin therapy, which is less than 10% of the total population. The former group of patients should have been referred to an NICU according to international guidelines,¹⁴ and the studied gentamicin dosing regimen was not intended to be used in these patients. In clinical practice, we suggest using a dosing algorithm specifically designed in a population of neonates with a GA <32 weeks. Although the sample size was too small to statistically compare the outcomes with neonates with a PNA <7 days at the initiation of therapy, preliminary results suggest that the dosing regimen may also show good performance in neonates with a PNA >7 days admitted to our level II unit.

One of the major strengths of this study is the combination of a prospective observational design with the minimal exclusion and loss of data reflecting real-life clinical practice. Second, 2 plasma samples were drawn at sampling times optimal for accurate estimation of PK parameters. Using this approach, for instance, C_{\min} and

TABLE 1. Dosing, Pharmacokinetics, and Target Attainment Rates

Dosing and PK Parameters	Mean (SD)
Gentamicin dose, mg	15.6 (4.0)
eC_{\max} , $\text{mg}\cdot\text{L}^{-1}$	10.8 (1.75)
eC_{\min} , $\text{mg}\cdot\text{L}^{-1}$	0.18 (0.12)
$eC_{24 \text{ h}}$, $\text{mg}\cdot\text{L}^{-1}$	0.64 (0.29)
AUC	99 (17.1)
Volume of distribution, $\text{L}\cdot\text{kg}^{-1}$	0.45 (0.075)
Half life, h	5.7 (1.1)
Clearance, $\text{L}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$	0.17 (0.051)
Target Attainment	Rate (%)
$C_{\max} > 8 \text{ mg}\cdot\text{L}^{-1}$	168/184 (91.3)
$C_{\min} < 0.5 \text{ mg}\cdot\text{L}^{-1}$	179/184 (97.3)
$C_{\max} > 8 \text{ mg}\cdot\text{L}^{-1}$ and $C_{\min} < 0.5 \text{ mg}\cdot\text{L}^{-1}$	166/184 (90.4)
$C_{\min} < 1 \text{ mg}\cdot\text{L}^{-1}$	184/184 (100)
$C_{24 \text{ h}} < 1 \text{ mg}\cdot\text{L}^{-1}$	158/184 (85.9)
$C_{24 \text{ h}} < 0.5 \text{ mg}\cdot\text{L}^{-1}$	95/184 (51.6)

Values are presented as mean with SD and ranges or as rates and percentages. AUC, area under the concentration-time curve of one dosing interval; $eC_{24 \text{ h}}$, estimated serum concentration 24 hours after the end of infusion; eC_{\max} , estimated maximum serum concentration; eC_{\min} , estimated minimum serum concentration.

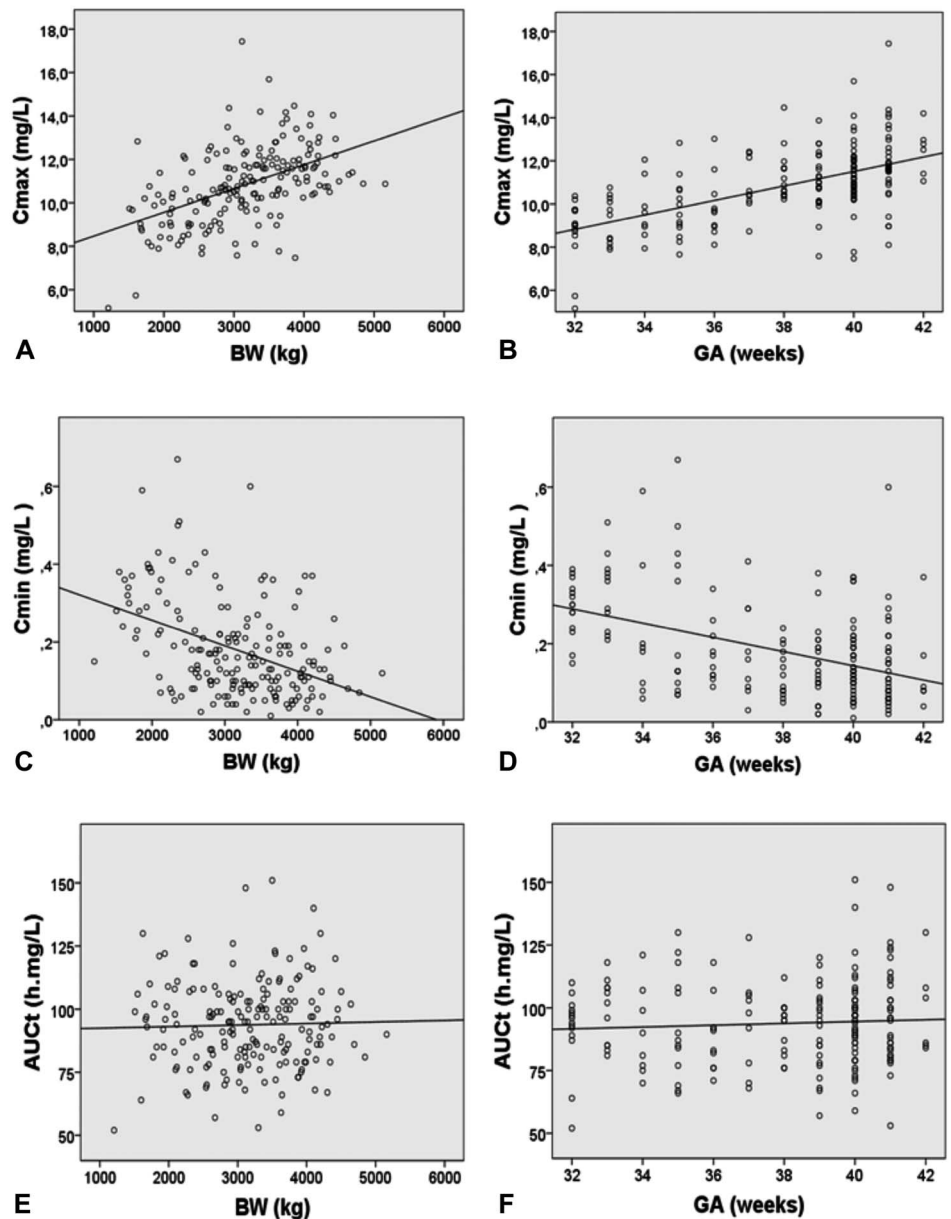


FIGURE 1. Correlations between BW, GA, and exposure parameters. Correlations (A) between BW and C_{max} ($r = 0.44$, $P < 0.001$), (B) between GA and C_{max} ($r = 0.58$, $P < 0.001$), (C) between BW and C_{min} ($r = 0.42$, $P < 0.001$), (D) between GA and C_{min} ($r = 0.50$, $P < 0.001$), (E) between BW and AUC_{τ} ($r = 0.064$, $P = 0.4$), and (F) between GA and AUC_{τ} ($r = 0.028$, $P = 0.7$) are depicted. AUC_{τ} , area under the concentration–time curve of one dosing interval.

AUC values can be accurately estimated instead of sampling actual trough concentrations that are unreliable because of a high assay error at low gentamicin concentrations.¹⁵ Limited AUC sampling offers the opportunity to identify individual CI next to the gentamicin “load” represented by the AUC. In this study, a mean gentamicin “load” expressed as the $AUC_{36\text{ h}}$ of $99\text{ mg}\cdot\text{h}\cdot\text{L}^{-1}$ was found, which is equivalent to an $AUC_{24\text{ h}}$ of $75\text{ mg}\cdot\text{h}\cdot\text{L}^{-1}$ that gives high chances of success and safety as proposed by Drusano et al.⁹

Interestingly, the high target attainment rates may call for a revision of the intensive drug concentration monitoring after the first dose in all neonates with GA >32 weeks and PNA <7 days. Sampling after the second dose could significantly reduce patients’ blood sampling burden because gentamicin is frequently administered for a short period of 36–72

hours in neonates.¹⁶ A further reduction in gentamicin course duration may be anticipated because the turnaround times of blood cultures have significantly been reduced in recent years. Especially, in combination with extended dosing interval dosing regimens, this could facilitate current practices of stopping gentamicin therapy earlier, perhaps even before the second dose.^{16–18} Thus, patients will not needlessly be exposed to gentamicin for longer periods but will also be refrained from both the pain and risk of infection associated to blood sampling in neonates. Two meta-analyses that comprise approximately 600 newborns have shown that irrespective of the dosing schedule in combination with routine aminoglycoside blood concentration monitoring, sepsis was clinically cured in almost every patient.^{19,20} In this context, one should realize that antibacterial courses are started in

newborns even with a low probability of sepsis. Although many studies did not find any aminoglycoside-related toxicity, (transient) hearing loss and renal tubular damage have been reported.^{19,21}

Because of the PK/pharmacodynamic profile of gentamicin and the rapid dose-dependent bacterial killing after the first dose, followed by adaptive resistance and a post-MIC effect, low trough concentrations do not necessarily lead to a poorer outcome. A relatively drug-free interval, as is common in adult populations, may reduce aminoglycoside-related toxicity and adaptive resistance in newborns.⁸ Hence, future clinical studies investigating the PK and risk/benefit ratio of dosing strategies aiming for drug-free periods ($C_{\min} < 0.5$ mg/L) in neonatal populations are warranted.

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