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Gentamicin Pharmacokinetics and Dosing in Neonates with Hypoxic Ischemic Encephalopathy Receiving Hypothermia

Adam Frymoyer^a, Lina Meng^b, Sonia L. Bonifacio^c, Davide Verotta^d, and B. Joseph Guglielmo^e

^aDepartment of Pediatrics, Stanford University

^bDepartment of Pharmacy, Stanford Hospital and Clinics

^cDepartment of Pediatrics, University of California, San Francisco

^dDepartment of Bioengineering and Therapeutic Sciences, University of California, San Francisco

^eDepartment of Clinical Pharmacy University of California, San Francisco

Abstract

Study Objective—To evaluate the pharmacokinetics of gentamicin in neonates with hypoxic ischemic encephalopathy (HIE) receiving hypothermia and to identify an empiric gentamicin dosing strategy in this population that optimizes achievement of target peak and trough concentrations.

Design—Population pharmacokinetic study using retrospective medical record data.

Setting—Tertiary neonatal intensive care unit.

Patients—A total of 29 term neonates diagnosed with HIE treated with hypothermia who received gentamicin and underwent therapeutic drug monitoring.

Measurement and Main Results—Patient demographics and gentamicin concentration data were retrospectively collected over a 2-year period. A population-based pharmacokinetic model was developed using nonlinear mixed-effects modeling (NONMEM). Using the developed model, Monte Carlo simulations were performed to evaluate the probability of achieving target peak (>6 mg/L) and trough (<2 mg/L) gentamicin concentrations for various potential dosing regimens. A one-compartment model best described the available gentamicin concentration data. Birthweight (BW) and serum creatinine (SCr) significantly influenced gentamicin clearance. For the typical study neonate (BW 3.3 kg; SCr 0.9 mg/dL), clearance was 0.034 L/H/kg and volume was 0.52 L/kg. At a 24-hour dosing interval, Monte Carlo simulations predicted target gentamicin peak and trough concentrations could not be reliably achieved at any dose. At a 36-hour dosing interval, a dose of 4–5 mg/kg is predicted to achieve target gentamicin peak and trough concentrations in >90% of neonates.

Conclusions—Gentamicin clearance is decreased in neonates with HIE treated with hypothermia compared with previous reports in nonasphyxiated normothermic term neonates. A prolonged 36-hour dosing interval will be needed to achieve target gentamicin trough

Correspondence & Reprints Department of Pediatrics Stanford University 750 Welch Rd, Suite #315 Palo Alto, CA 94304 Phone: +1 650 723-5711 Fax: +1 650 725-8351 frymoyer@stanford.edu.

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concentrations in this population. Further prospective evaluation of this dosing recommendation is needed.

Keywords

gentamicin; neonates; pharmacokinetics; hypothermia; hypoxic ischemic encephalopathy

INTRODUCTION

Gentamicin is commonly used in neonates with hypoxic ischemic encephalopathy (HIE) for the empiric treatment of presumed infection. The drug displays concentration-dependent killing and clinical response is associated with the ratio of the peak concentration over the MIC (peak/MIC).^{1,2} However, prolonged high drug concentrations are associated with nephrotoxicity and therapeutic drug monitoring (TDM) is routinely performed to document drug clearance. Every 24-hour dosing of gentamicin in full-term neonates takes advantage of these drug properties and is superior to multiple-daily dosing in terms of achievement of higher peak concentrations and lower trough concentrations.³

In neonates with HIE, gentamicin pharmacokinetics may be altered. Gentamicin is eliminated almost exclusively by glomerular filtration⁴ and neonates with HIE often have acute kidney dysfunction.^{5–9} In addition, hypothermia—an effective treatment modality for HIE¹⁰—may cause additional alterations in organ physiology and blood flow that impact drug pharmacokinetics.¹¹ But, in a recent clinical study of hypothermic versus normothermic neonates with HIE, both groups had similar trough concentrations, suggesting little effect of hypothermia on gentamicin pharmacokinetics. However, both groups frequently had elevated trough concentrations >2 mg/L when receiving gentamicin 4–5 mg/kg every 24 hours (44% of normothermic and 36% of hypothermic).¹² This highlights the need for a potential alternative dosing of gentamicin in the neonate with HIE. Given that hypothermia is now recommended as the standard of care for moderate to severe HIE,¹³ an understanding of gentamicin pharmacokinetics in the clinical context of hypothermia will be necessary to help guide dose selection in this population. The objectives of this study were 1) to evaluate the pharmacokinetics of gentamicin in neonates with HIE receiving hypothermia using a population-based approach and 2) to identify an empiric gentamicin dosing strategy that optimizes achievement of target peak and trough drug concentrations.

METHODS

We conducted a retrospective chart review in neonates with presumed HIE treated with whole-body hypothermia (33.5°C) at a fifty-bed level III neonatal intensive care unit (NICU) located in a tertiary care, academic medical center from November 2007 to March 2010. This study was approved by the UCSF Committee on Human Research. Eligibility criteria for hypothermia for neonates <36 weeks gestational age have been previously described.¹⁴ For those neonates with HIE who underwent gentamicin TDM during hypothermia, clinical and laboratory data were collected, including complete gentamicin dosing and drug level history. Neonates were excluded if gentamicin drug levels or a complete gentamicin dosing history was not available, extracorporeal membrane oxygenation (ECMO) was required during the gentamicin course, or congenital heart disease or kidney disease was diagnosed. The recommended gentamicin dose at UCSF for neonates with HIE during the period of study was 5 mg/kg every 24 hours. Each dose was administered intravenously over 30 minutes. For newborns continued on gentamicin >48h, TDM at the third or fourth dose was recommended. Gentamicin drug levels were obtained prior to the third dose at the discretion of the clinical team (i.e. if there was concern about altered renal function). Target peak concentrations were >6 mg/L and target trough

concentrations were <2 mg/L. Gentamicin trough concentrations were drawn just prior to the next dose and peak concentrations were drawn 30 minutes after the end of infusion.

Quantitative determination of gentamicin serum concentrations was performed by the UCSF Clinical Laboratory using a competitive immunoassay (ADVIA Centaur Gentamicin assay, Bayer Diagnostics, Deerfield, IL). The reportable range of the assay was 0.2 mg/L to 24 mg/L. The within-run and between-run coefficient of variation for the assay was less than 8%.

Population Pharmacokinetic Analysis

A population pharmacokinetic model was developed from the gentamicin concentration time data using the nonlinear mixed-effects modeling program NONMEM (Version VII, Icon Development Solutions). The first order conditional estimation method with interaction was used throughout the model building and evaluation process. A one-compartment pharmacokinetic model with first-order elimination was implemented. Interindividual variabilities were evaluated on clearance (CL) and volume of distribution (V), using an exponential error model. To model the residual variability (i.e. intra-individual or “measurement error” that captures the difference between the model predicted concentration for an individual and the observed concentration in that individual) both additive and proportional error models were evaluated. Selection between models was based on the difference in the NONMEM objective function value (OFV) and visual comparison of standard diagnostic plots. The difference in OFV between two models has an approximate χ^2 distribution with degrees of freedom equal to the difference in the number of parameters between models. Significance was set at a decrease in OFV larger than 10.83, corresponding to a $p < 0.001$.

Once the structural pharmacokinetic model was established, biologically or clinically plausible covariates were evaluated for their influence on pharmacokinetic parameters. Based on previous population pharmacokinetic modeling for a range of compounds in neonates and children, the effect of birthweight on clearance and volume of distribution was implemented using an allometric model with the exponent defining the relationship fixed to 0.75 and 1, respectively.¹⁵ Continuous covariates were then examined for their influence on clearance, including gestational age, serum creatinine (SCr) on postnatal age (PNA) Day 1 (corresponding to the second day of life for the infant), and first blood pH. The effect of a continuous covariate on a parameter was modeled assuming an exponential relationship. Continuous covariates were scaled to their median values. Categorical covariates evaluated were concomitant dopamine and APGAR 5 at 10 minutes. Categorical covariates were modeled proportionally, i.e. the fractional change in clearance when the categorical covariate was true.

The covariate model was built using a standard forward addition backward deletion procedure. Covariates were added in a stepwise manner to the model in the order of their reduction in the OFV. During forward stepwise addition, a covariate was allowed to enter the model as long as the decrease in OFV resulting from its addition was larger than 3.84, corresponding to a $p < 0.05$. After the stepwise addition terminates, the model is pruned using backward elimination. Covariates were eliminated one at a time, until the removal of a covariate results in an OFV increase of more than 10.83, corresponding to a $p < 0.001$.

To evaluate the accuracy and stability of the final pharmacokinetic model, a non-parametric bootstrap re-sampling method was performed using the NONMEM software interface PLT Tools (Version 3.5.1, PLTsoft). A total of 1000 bootstrap datasets were generated from the original data set by repeated sampling with replacement, and the final pharmacokinetic model was used to estimate model parameters for each of the 1000 data sets. In addition, a visual predictive check (VPC) was performed. The final PK model was used to simulate

approximately 1000 gentamicin peak and trough concentrations, and the distributions of simulated and observed data were then compared. All concentrations were dose normalized to a gentamicin dose of 5 mg/kg.

Monte Carlo Simulations

To evaluate empiric gentamicin dosing regimens in terms of the probability of achieving target peak and trough gentamicin levels, a Monte Carlo simulation analysis was conducted. Simulations of 5000 'hypothetical' neonates were conducted for each dosing regimen using Crystal Ball version 11.1.1.1.00 (Oracle Corporation, Redwood Shores, California). The final population pharmacokinetic model was used for simulations. To incorporate increased variability likely to be seen in a larger population, the coefficient of variation (CV%) for clearance and the residual variability were set to 20%, which was within the 95% confidence interval for each parameter estimate as found by bootstrap. Variability in birthweight was incorporated using distributions from the Center for Disease Control and Prevention.¹⁶ Variability in serum creatinine was based on the distribution in the current study population truncated at a minimum of 0.5 mg/dL and a maximum of 1.5 mg/dL. Doses ranging from 3 to 5 mg/kg were assessed at dosing intervals of 24, 36, and 48 hours. In addition, a sensitivity analysis was conducted to evaluate the influence of serum creatinine on PNA Day 1 on the achievement of trough gentamicin concentration <2 mg/L. Monte Carlo simulations were conducted as described above; however, the dose was held constant while the serum creatinine on PNA Day 1 was adjusted from 0.5 to 1.5 mg/dL between simulations.

RESULTS

Subjects and Gentamicin Drug Levels

In total, 34 neonates with HIE receiving hypothermia had gentamicin concentration data available. Five neonates were excluded: three required ECMO, one was diagnosed with cardiomyopathy, and one had an incomplete dosing record. A total of 47 gentamicin concentrations from the remaining 29 neonates were included in the population pharmacokinetic analysis (18 had peak and trough concentrations; 11 had trough concentrations only). Neonate characteristics are presented in Table 1. The empiric gentamicin dose was 5 mg/kg every 24 hours for 25 neonates, 4.5 mg/kg every 24 hours for 1 neonate, and 4 mg/kg every 24 hours for 3 of the neonates. Therapeutic drug monitoring was performed at the second, third and fourth dose in 10, 12, and 7 patients, respectively. The median initial trough concentration was 1.8 mg/L (interquartile range [IQR], 1.4 - 2.6 mg/L) with a minimum trough concentration of 1 mg/L and maximum trough concentration of 3.6 mg/L. Eleven patients (38%) had an initial trough concentration $\geq$ 2.0 mg/L. The median initial peak concentration was 11.3 mg/L (IQR, 9.9 - 12.6 mg/L) with a minimum peak concentration of 7.5 mg/L and maximum peak concentration of 15.3 mg/L. All subjects had an initial peak concentration $\geq$ 6.0 mg/L. The median duration of gentamicin therapy was 6 days (IQR, 4 – 7 days).

Population Pharmacokinetic Analysis

Gentamicin concentrations were adequately described by a one-compartment model with first-order elimination. Interindividual variability for volume could not be estimated with any precision using the available data. Removal of this random effect on volume did not change the statistical fit of the model or the goodness of fit plots, and therefore, it was removed from the model. Only interindividual variability for clearance was incorporated into the final model. The residual variability (or intraindividual variability) was best described by a proportional error model.

After incorporating the allometric model of birthweight on clearance and volume, covariate selection identified SCr as a significant predictor of gentamicin clearance ($p < 0.001$). No other covariates examined significantly affected gentamicin clearance. The final population pharmacokinetic model parameter estimates are presented in Table 2. In general, observed-versus population-predicted concentrations showed no systemic bias, and the weighted residuals were homogeneously scattered (Figure 1). The parameter estimates as found by bootstrap were in agreement with those obtained by the final population pharmacokinetic model (Table 2), indicating reliability of the final model estimates. The VPC also demonstrated that the final model performed reasonably well in describing the observed data (Figure 2). Neonates with an elevated SCr on PNA day 1 were estimated to have lower gentamicin clearance. For example, a typical neonate with SCr 1.4 mg/dL had a clearance 27% lower than a neonate with SCr 0.8 mg/dL.

Monte Carlo Simulations

Predicted gentamicin peak and trough concentrations at various gentamicin dosing regimens are shown in Table 3. At 24 hour dosing, target achievement of steady-state gentamicin trough concentrations < 2 mg/L were not reliably achieved at any dose (Figure 3a). For both 36- and 48-hour dosing, more than 90% of simulated neonates were predicted to achieve target steady-state trough concentration < 2 mg/L at all dose strengths (3 to 5 mg/kg). Target peak concentrations after the first dose > 6 mg/L were achieved in more than 90% with doses of 4.5 and 5 mg/kg (Figure 3b). At steady-state the minimum dose needed to achieve peak concentrations > 6 mg/L in more than 90% of subjects was 4 mg/kg at 24- or 36-hour dosing and 4.5 mg/kg at 48-hour dosing (Figure 3c).

Sensitivity analysis showed that at a dose of 5 mg/kg every 36 hours, achievement of target trough concentrations < 2 mg/L declined at higher SCr (Figure 4). For example, at SCr 1.3 mg/dL, the proportion of neonates achieving target trough concentration fell below 80%. At a dose of 5 mg/kg every 48 hours, the results were not influenced by SCr.

DISCUSSION

Gentamicin is one of the most common antibiotics used in neonates to treat suspected sepsis.¹⁷ Accordingly, the pharmacokinetics of gentamicin in neonates has been frequently studied and standard every 24-hour dosing regimens for term and preterm neonates have been recommended.^{18,19} However, neonates are a highly variable group, and in addition to size and maturation, disease state can have an impact on drug pharmacokinetics. In a recent study of term neonates with HIE receiving gentamicin doses of 4-5 mg/kg every 24 hours, both hypothermic and normothermic neonates frequently had gentamicin trough concentrations > 2 mg/L.¹² Data from our current study corroborate that earlier data, with 38% of hypothermic neonates with HIE having a gentamicin trough concentration > 2 mg/L when receiving a median gentamicin dose of 5 mg/kg every 24 hours. This high rate of elevated trough concentrations in the HIE population with standard daily doses of gentamicin suggests the need for alternative dosing strategies. However, the pharmacokinetics of gentamicin in this group, which are necessary to guide any alternative dosing strategies, have not been formally investigated. Under this context, we developed a population pharmacokinetic model of gentamicin in neonates with HIE receiving hypothermia using retrospective clinical data. We then used this quantitative model to simulate and predict an empiric gentamicin dosing regimen that would maximize achievement of target peak and trough concentrations.

The final population pharmacokinetic model described the gentamicin plasma concentrations reasonably well. For the typical neonate in our study (BW 3.3kg, SCr 0.9 mg/dL), gentamicin clearance was 0.118 L/H (0.036 L/h/kg). This estimate of clearance is 25%

to 50% lower than previous reports in term non-asphyxiated, normothermic neonates.^{20–24} The volume of distribution found in our study (0.47 L/kg) was similar to previous reports.^{20–24}

Gentamicin's major route of elimination is via glomerular filtration.⁴ Therefore, patient specific factors that characterize kidney function may help explain interindividual variation in gentamicin clearance. In our study, birthweight was a significant predictor of clearance; body size is a well-known scalar of glomerular filtration in children and neonates.^{15,25} Postnatal age^{22,26,27} and gestational age^{27,28} can help characterize the maturation of renal drug clearance in the developing neonate. Gestational age did not affect clearance in our study and this was likely due to the narrow range of gestational ages intrinsic to our institution's eligibility criteria for hypothermia (< 36 weeks). Since all neonates were of the same postnatal age $\pm$ 1 day, we were unable to examine this effect.

While SCr is the most common method to monitor kidney function, it is generally regarded as a poor indicator in the first 24 to 48 hours after birth due to placental transfer. But in our study, SCr on PNA day 1 was a predictive marker of clearance. We hypothesize that this predictive ability of SCr may be due to a large number of neonates (~30%) with an SCr 1.2 mg/dL in our study. When SCr is elevated beyond what would be expected due to placental transfer from a healthy pregnant women (reference range 0.4 – 0.9 mg/dL),²⁹ it may provide predictive information on kidney function in the neonate. Several previous population pharmacokinetic studies in neonates have also found that SCr influences gentamicin clearance,^{24,26,28} while one study did not.²⁷

Additional limitations of SCr as a biomarker of kidney function include its poor sensitivity in detecting mild to moderate kidney injury and a delay in SCr rise after injury.³⁰ Therefore, we also examined first pH, 10 minute APGAR, and the need for concomitant dopamine as markers of disease severity that could impact kidney function. None were associated with gentamicin clearance. Newer urinary biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), are promising in preterm and postcardiopulmonary bypass neonates to predict early acute kidney injury.^{31–33} Their potential role in neonates with HIE is unknown and further research in this area may be helpful in understanding acute kidney injury and drug dosing needs in the HIE population. We were unable to evaluate the independent impact of hypothermia on gentamicin pharmacokinetics since all neonates in our study were cooled. Previous animal studies have shown a 50% decrease in gentamicin clearance during severe hypothermia (29°C)³⁴ but no difference in clearance during moderate hypothermia (35°C).³⁵ The only available clinical study reported no difference in serum gentamicin trough concentrations between normothermic and hypothermic (33.5°C) neonates with HIE.¹² While understanding the independent effect of hypothermia on gentamicin pharmacokinetics is valuable, hypothermia is now the standard of care for the HIE population. Therefore it will be challenging to characterize this independent effect in the HIE population moving forward. It is still, however, essential to investigate drug pharmacokinetics for the HIE population in the context of hypothermia. This is highlighted by the known alterations in drug concentrations from the few clinical drug studies performed in this population.¹¹

Our Monte Carlo simulations demonstrated that to consistently achieve trough concentrations < 2mg/L, an empiric gentamicin dose of 4-5 mg/kg every 36 hours is needed. A 48-hour dosing interval was also predicted to achieve target peak and trough concentrations, but there are potential concerns regarding gentamicin efficacy during prolonged periods of low serum concentrations that would occur with a 48-hour dosing interval. For example, with 48 hour dosing, more than 25% of neonates would be predicted to have a gentamicin concentration < 0.5 mg/L for the last 12 hours of the dosing interval. A

waning postantibiotic effect during this time may allow for bacterial regrowth to occur for gram-negative pathogens with MIC $\geq 0.5\text{mg/L}$.³⁶ A dosing interval of 36 hours minimizes this potential efficacy concern while still achieving the benefit of reduced gentamicin accumulation. Dosing intervals greater than 24 hours have previously been described for other neonatal populations with reduced gentamicin clearance, such as the preterm neonate.³⁷ Therefore, we recommend an empiric gentamicin dose of 4-5 mg/kg every 36 hours in neonates with HIE receiving hypothermia, and we have recently implemented this new dosing protocol in our NICU. Routine TDM at the third dose for those continuing a treatment course of gentamicin is still recommended due to the heterogeneity of the HIE population. Alternatively, a gentamicin concentration at 24h after the first dose can be measured and used to help guide further dosing.

Limitations to our study include the retrospective design and the use of a convenience sample of drug level data collected as part of routine care. However, the population technique is well suited to account for underlying variation in individual data. Additional limitations include the use of single center data and lack of a validation group due to the small sample size of patients available for study. The general agreement of our data with the only other prior report of gentamicin concentrations in the HIE population is reassuring,¹² but further validation of our model is warranted.

Conclusions

In neonates with HIE receiving hypothermia, gentamicin trough concentrations $> 2\text{mg/L}$ are frequent with 5 mg/kg every 24 hours dosing. This is likely due to reduced gentamicin clearance in this population. An empiric dose of 4-5 mg/kg every 36 hours is predicted to optimize achievement of target peak and trough concentrations. Further dosing adjustments may be required in neonates with acute renal injury and can be guided by TDM. Additional pharmacokinetic studies are needed in neonates with HIE receiving hypothermia given the frequent alterations in drug disposition described in this vulnerable population.

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Figure 1. Goodness of fit plots for the final population pharmacokinetic model: a) observed versus population predicted gentamicin concentrations (mg/L); b) weighted residual versus population predicted gentamicin concentration (mg/L).

Figure 2. Visual predictive check of the final population pharmacokinetic model. The 5th, 50th and 95th percentiles for 1000 simulated gentamicin concentrations are presented along with the observed data. Concentrations are dose-normalized to a 5 mg/kg gentamicin dose.

Figure 3. Achievement of target drug concentrations at various gentamicin dosing regimens in neonates with HIE receiving hypothermia. At each dose, Monte Carlo simulation was performed (n=5000), and the fraction of neonates predicted to achieve a) trough concentration <2 mg/L at steady-state, b) peak concentration >6 mg/L after the first dose, and c) peak concentration >6 mg/L at steady-state are shown for dosing intervals of 24 hours, 36 hours and 48 hours.

Figure 4. Sensitivity analysis of the effect serum creatinine (mg/dL) on postnatal age (PNA) day 1 on the achievement of gentamicin trough concentration <2 mg/L at steady-state. A dose of 5mg/kg at intervals of 24 hours, 36 hours and 48 hours was assessed by Monte Carlo simulation.

Table 1

Patient Demographics (n = 29)

	Median or No.	IQR
Gestational age, wks	40.0	37.6 – 40.7
Birthweight, kg	3.32	2.97 – 3.50
Female	18 (62%)	
APGAR 5 min 10 min	3 5	1 – 4 3 – 6
First arterial or capillary pH	7.0	6.9 – 7.1
Base Deficit, mmol/L	–19	–15 – –27
Serum creatinine on PNA Day 1*, mg/dL	0.9	0.8 – 1.2
Assisted Ventilation, n (%)	24 (83%)	-
Seizures, n (%)	16 (55%)	-
Dopamine, n (%)	18 (62%)	-
Death prior to discharge, n (%)	6 (21%)	-

PNA=postnatal age

Table 2

Final population PK model parameter estimates.

Population PK Parameters	Final Model		Bootstrap (n=1000)	
	Estimate	RSE (%)	Median	95% CI ^I
Typical Value of CL ² (L/h)	0.111	4.2	0.111	0.103 – 0.121
Exponent accounting for SCr effect on CL	0.566	21.9	0.572	0.347 – 0.839
V (L)	1.56	4.7	1.55	1.42– 1.72
Inter-individual variability of CL, %CV	16.1	30.5	15.3	2.7 – 19.8
Residual variability, %CV	16.2	24.1	15.8	11.7 – 22.4

PK= pharmacokinetic; RSE= relative standard error; CL= clearance; V= volume of distribution; SCr= serum creatinine (mg/dL); %CV= coefficient of variation × 100.

^I 95% CI corresponding to parameter estimates at the 2.5th and 97.5th percentiles of 1000 bootstrap runs.

$$\text{CL (L/h)} = 0.111 \times \left(\frac{\text{Birthweight}}{3.3\text{kg}} \right)^{0.75} \times \left(\frac{1}{\text{Cr}_{\text{mg/dl}}} \right)^{0.566}$$

Table 3

Predicted gentamicin peak and trough concentrations (mg/mL) at steady-state from Monte Carlo simulations (n=5,000) with various dosing regimens. Median (10%, 90%) reported.

	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-hour interval	7.1 (5.1, 9.4)	1.4 (0.6, 2.7)	8.2 (5.9, 11.0)	1.6 (0.7, 3.1)	9.4 (6.8, 12.5)	1.8 (0.8, 3.6)	10.6 (7.6, 14.1)	2.1 (0.9, 4.0)	11.8 (8.5, 15.7)	2.3 (1.0, 4.5)
36-hour interval	6.3 (4.7, 8.1)	0.5 (0.2, 1.2)	7.4 (5.4, 9.5)	0.6 (0.2, 1.4)	8.4 (6.2, 10.8)	0.7 (0.2, 1.6)	9.5 (7.0, 12.2)	0.8 (0.3, 1.8)	10.5 (7.8, 13.5)	0.9 (0.3, 2.0)
48-hour interval	6.0 (4.4, 7.7)	0.2 (0.1, 0.6)	7.0 (5.1, 8.9)	0.2 (0.1, 0.7)	8.0 (5.9, 10.2)	0.3 (0.1, 0.8)	9.0 (6.6, 11.5)	0.3 (0.1, 0.9)	10.0 (7.3, 12.8)	0.4 (0.1, 1.0)