Protocol: Extended Interval Dosing of Gentamicin in Neonates

London Health Sciences Centre

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Background:

The current study will be examining the use of Extended Interval Dosing (EID) of Gentamicin in Neonates to determine if target serum gentamicin concentrations are being achieved with current dosing at the Children's Hospital at London Health Sciences Centre (LHSC). This study is a continuation of the initial 2005-2006 pharmacy residency project conducted by Anna Yun (Phase I & II), followed by Phase III conducted by Dr. Venita Harris.

Gentamicin is an aminoglycoside antibiotic with concentration dependent kinetics (1,2). Dose optimization is needed to ensure pharmacokinetic trough and peak targets are met given the narrow therapeutic index of gentamicin, while minimizing the risk of nephrotoxicity and ototoxicity (1). Elevated gentamicin troughs can contribute to nephrotoxicity, whereas cumulative dose and duration of gentamicin may contribute to ototoxicity (1). Neonates have a higher proportion of body water and given that aminoglycosides are water soluble, this means higher doses of gentamicin are required in neonates (3,4). Various dosing strategies are available for gentamicin. Traditional dosing (TD) involves more frequent dosing, whereas EID involves gentamicin dosed less frequently, such as once daily, which takes into consideration that kidney function is still developing in the neonate with a reduced ability to clear gentamicin (1,3). Of note, EID in neonates differs from adult EID where higher doses of gentamicin are given less frequently to reach high concentrations that would not be reached in neonates (2,5).

In the 2005-2006 pharmacy residency year, Anna Yun conducted a prospective research study in neonates ages 0-7 days. Phase I evaluated gentamicin TD 2.5 mg/kg q18h (28-34 weeks gestational age) and 2.5 mg/kg q12h for > 34 weeks gestational age (combined n = 21). Phase II evaluated gentamicin EID 3 mg/kg q24h in neonates at least 28 weeks gestational age (n = 21) (6). Prior to the prospective component of the study, TD was standard of care at the Children's Hospital of Western Ontario nursery and Paediatric Critical Care Unit and St. Joseph's Health Care London Neonatal Intensive Care Unit with an initial retrospective analysis indicating a high proportion of trough levels out of target range. A prospective multi-phase quality improvement initiative was then conducted at the same sites for neonates up to 7 days of age, at least 28 weeks gestational age, and receiving gentamicin. TD of gentamicin was then prospectively assessed with an interim analysis planned. If troughs were within range 80-90% of the time, the study would end and EID would not be implemented nor analyzed. This analysis showed that EID was needed with pharmacokinetic extrapolations used to determine the EID dosing regimen. The analysis compared the following dosing regimens: gentamicin 2.5 mg/kg q24h, 3 mg/kg q24h, 3.5 mg/kg q24h, and 4 mg/kg q24h. Gentamicin 3 mg/kg q24h was the appropriate dosing regimen chosen for EID based on the pharmacokinetic analysis. When comparing the two regimens, TD showed significantly higher mean troughs (1.81 +/- 0.76 mg/L) compared to EID (0.52 +/- 0.29 mg/L, $p < 0.001$) and a higher proportion of troughs out of range in TD (42.9%) vs EID (0%, $p = 0.001$). Mean peak concentration in TD was 7.76 +/- 1.86 mg/L and was not statistically different from mean peak concentration in EID (7.48 +/- 1.29 mg/L, $p = 0.53$). Both

TD and EID achieved high proportions of peaks in reference range, at 85.7% and 90.5% respectively. No nephrotoxicity or ototoxicity was identified in either group.

Phase III of the study was conducted by Venita Harris evaluating EID at dosing which reflects current dosing with neonates 0-7 days < 35 weeks gestational age dosed at 3 mg/kg q24h (n = 29) and ≥ 35 weeks at 3.5 mg/kg q24h (n = 21). Mean trough was 1.04 +/- 0.43 mg/L and 0.51 +/- 0.40 mg/L for the 3 mg/kg q24h and 3.5 mg/kg q24h regimens, respectively. Mean peak was 8.18 +/- 1.10 mg/L and 8.91 +/- 2.06 mg/L for the 3 mg/kg q24h and 3.5 mg/kg q24h regimens, respectively. Troughs were within reference range 97% of the time with the 3 mg/kg q24h regimen and 100% of the time with the 3.5 mg/kg q24h regimen. Peaks were within reference range 97% of the time with the 3 mg/kg q24h regimen and 71% of the time with the 3.5 mg/kg q24h regimen. Notably, for the 3.5 mg/kg q24h regimen, most of the peaks outside of reference range were due to elevated peaks rather than subtherapeutic peaks. The current study will further validate if the dosing of gentamicin is still achieving target trough and peak levels, and how this might compare to the values found historically in the past phases. The study will collect baseline information pertaining to usual care. This baseline information includes age (postnatal age), gestational age, APGAR scores at 1 and 5 minutes, birth weight, weight at time of gentamicin initiation if different than birth weight, sex, other nephrotoxic or ototoxic drugs, medical conditions, reason for admission, and indication for gentamicin. Cultures will be recorded for results within 48 hours before or after the first dose of gentamicin. Culture results will be recorded for blood, urine, central nervous system (lumbar puncture), and any other cultures. The collection site will be recorded, including central, peripheral, or cord for blood cultures, catheter, suprapubic aspiration, or clean catch for urine cultures, and collection site description for other culture results. No growth or growth will be recorded per available culture result. If growth is found, the microbiology result will be recorded.

The literature includes many studies examining EID of gentamicin in neonates. The Cochrane Meta-analysis included 11 trials (n = 574 neonates) comparing one dose per day to multiple doses per day of gentamicin in neonates for treatment of suspected or proven sepsis (7). Doses ranged from 4-5 mg/kg/day either as one dose per day or divided doses. Main findings showed that once-a-day dosing had fewer failures in achieving target peak (5 mg/L) and trough (≤2 mg/L) levels compared to the multiple dose regimen. No statistically significant differences in ototoxicity were reported between groups and nephrotoxicity was not detected in either group. A different study examined six different EID regimens through a retrospective study conducted in the Neonatal Intensive Care Unit at St. Luke's Regional Medical Center in Iowa (8). EID regimens of gentamicin in neonates (n = 304 neonates) were as follows: 29 weeks or younger for gestational age at 4.5 mg/kg q48h, 30-34 weeks gestational age at 3.5, 4, or 4.5 mg/kg q36h, and 35 weeks or older at 3.5 or 4 mg/kg q24h (8). The authors found no significant difference in trough levels within reference range between the different dosing regimens for each gestational age group. The dosing regimens that reached favourable target peak levels were as follows: 3.5 mg/kg q36h for gestational age 30-34 weeks and 3.5 mg/kg q24h for gestational age 35 weeks or

older. Of note, the latter regimen aligns with the current LHSC dosing for neonates of gestational age 35 weeks or older. A randomized-controlled trial was conducted by a different research team evaluating the dosing of gentamicin EID regimen of 5 mg/kg q36h in neonates as the intervention compared to TD control group (9). Two subgroups were identified, including gestational age 34 weeks or less (n = 25 per treatment and control groups) and 35 weeks and greater (n = 23 per treatment and control groups). Treatment failures did not occur in any participants. Both subgroups showed a trend in reducing elevated gentamicin trough levels with EID and a statistically significant reduction for gestational age 35 weeks or greater. Trough levels were significantly lower in EID versus TD group. The TD group also required more dosage changes compared to the EID group. The authors were able to conclude that gentamicin 5 mg q36h could reach target gentamicin levels with a simplified, less frequent dosing regimen. A q36h regimen poses challenges to nursing for timing of gentamicin and corresponding levels, especially in the context of shift changes. Thus, the current LHSC gentamicin regimen with q24h tends to be more convenient and less error prone.

Gentamicin dosing in neonates varies depending on institution. The Children's Hospital of Eastern Ontario (CHEO) "Neonatal Drug Therapy Manual" provides gentamicin dosing in neonates as follows: < 30 weeks gestational age and postnatal age 0-14 days at 5 mg/kg/dose q48h, 30-34 weeks gestational age and postnatal age 0-10 days at 5 mg/kg/dose q36h, ≥ 35 weeks gestational age and postnatal age 0-7 days 4 mg/kg/dose q24h (10). SickKids dose for gentamicin in neonates is as follows: < 34 weeks postmenstrual age and age 0-7 days at 3 mg/kg/dose q24h, and ≥ 34 weeks postmenstrual age and age 0-7 days at 3 mg/kg/dose q18h (11). Both hospital guidelines reference several studies, including two larger studies (12,13). A retrospective cohort study (n = 993) was conducted examining EID with gentamicin 4 mg/kg IV q24h for infants in all gestational ages other than < 28 weeks where 4 mg/kg IV q36h was used (12). Overall, the median trough level in all infants was 1.3 mg/L (interquartile range of 0.8-1.7) with 10.2% of trough levels > 2 mg/L with the study demonstrating feasibility of the EID dosing regimen. The other study was a prospective cohort design conducted among neonates admitted to the level II neonatal nursery treated for suspected early-onset sepsis (n = 184) (13). EID with gentamicin 5 mg IV q36h was studied. The authors found that the majority of neonates reached target concentrations with target Cmax > 8 mg/L and Cmin < 0.5 mg/L in 90.4% of neonates.

The current project is Phase IV of the LHSC study and will focus on determining if current gentamicin dosing (neonates 0-7 days < 35 weeks gestational age dosed at 3 mg/kg q24h and ≥ 35 weeks at 3.5 mg/kg q24h) can achieve target troughs and peaks in reference range in neonates (14). Gentamicin is often prescribed for empiric gram negative coverage for sepsis in combination with ampicillin (14). Given the empiric nature of gentamicin use in the majority of cases, it is predicted that cultures will be mostly negative. Thus, the focus of the study will be on pharmacokinetics and not on infectious disease culture results.

Rationale:

- Current gentamicin dosing at the Children's Hospital is based on the previous projects completed at LHSC.
- Different gentamicin dosing recommendations exist depending on the reference used.
- This study would help validate if the current dosing is still achieving target gentamicin concentration levels.
- We will compare the results of the current study to our historic data

Research Question:

Is the current gentamicin dosing suitable for the neonatal population at the Children's Hospital at London Health Sciences Centre?

Primary Objective:

The primary objective is to measure and monitor the number of trough gentamicin levels within target range < 2 mg/L with the current EID regimen compared to TD in neonates ≤ 7 days of age.

Secondary Objectives:

- Maintain peak gentamicin levels within target range (6-10 mg/L)
- Monitor the incidence of suspected nephrotoxicity (serum creatinine > 53 umol/L, Blood Urea Nitrogen (BUN) > 10 mmol/L, and urine output < 1 mL/kg/h)
- Monitor the incidence of suspected ototoxicity (failed on newborn hearing screening) in different dosing regimens. Newborn hearing screening tests follow electrophysiological methods with automated distortion product otoacoustic emissions and automated auditory brainstem response (15).

Study Design:

- Prospective cohort study conducted at the Children's Hospital at LHSC with patients admitted to Neonatal Intensive Care Unit (NICU), Paediatric Critical Care Unit (PCCU), or Paediatrics Unit (B6)
- If the infant meets the study inclusion criteria, a letter of information will be provided to the parent(s)/guardian(s) using REDCap. Consent must be obtained prior to enrollment.

Inclusion Criteria	***Exclusion Criteria***
• Neonates up to 7 days of age • Neonates must be on gentamicin • Gentamicin trough and peak levels must be available for the third dose of gentamicin	• Incorrect dose for weight (+/- 10% allowed to account for dose rounding) • Multiple levels from the same patient; only the first set of levels will be collected • Baseline renal dysfunction (e.g. congenital kidney disease)

	• On other nephrotoxic or ototoxic drugs concurrently with the first 3 days of gentamicin

- Neonates empirically treated for sepsis are often started on ampicillin and gentamicin as standard of care. The medical team orders gentamicin with LHSC standard of care recommending dosing at 3 mg/kg q24h in neonates < 35 weeks gestational age, 3.5 mg/kg q24h in neonates 35 weeks of gestational age or greater. Gentamicin levels (trough/peak) are routinely ordered for before and after the third dose if gentamicin is continued for more than 48 hours.
- It is at the discretion of the medical team to further order gentamicin levels for future doses for the purpose of therapeutic drug monitoring. Usually, if blood cultures are negative at 48 hours, gentamicin is discontinued and no gentamicin serum concentrations are required.

<u>Processes involved in collecting gentamicin levels and administering gentamicin</u>:

- Trough levels are measured within 30 minutes of the third dose
- Gentamicin is administered as a slow intravenous intermittent infusion over approximately 30 minutes
- Peak levels are measured 30 minutes after the end of the flush following the third dose (14,16).
- No gentamicin dose adjustments based on levels will have been made prior to this point and will follow gentamicin dosing of 3 mg/kg q24h in neonates < 35 weeks gestational age and 3.5 mg/kg q24h in neonates 35 weeks of gestational age or greater
- The corresponding times/dates are recorded by nursing for trough and peak blood draws and infusion start and stop times.

<u>Laboratory measurements</u>*:*

- Analysis method: Enzyme immunoassay (EIA) performed by Core Lab and reported on Cerner Powerchart Electronic Medical Record (16,17)
    - *Lower limit of quantification: 0.24 mg/L*
        - Any concentration values lower than 0.24 will be substituted for the value of "0.23". A one-sample t-test will be conducted comparing the mean concentration calculated with the substituted value of 0.23 against a mean excluding all infants with concentrations below 0.24. If no significant difference is found, the substituted "0.23" concentration will be used in place of concentrations below 0.24 for further analyses. However, if a significant difference is found, two separate analyses will be conducted. The analysis including the substituted "0.23" value(s) may not accurately

reflect the sample, whereas excluding values under 0.24 will result in being underpowered for the other analysis.

- *Upper limit of quantification:* 12 mg/L; the upper limit is typically 12 mg/L; however, the lab will do a manual dilution up to 24 mg/L for any concentrations above 12 mg/L.
    - Any concentration values above 24 will be substituted for the value of "25". A one-sample t-test will be conducted comparing the mean concentration calculated with the substituted value of 25 against a mean excluding all infants with concentrations above 24. If no significant difference is found, the substituted "25" concentration will be used in place of concentrations above 24 for further analyses. However, if a significant difference is found, two separate analyses will be conducted. The analysis including the substituted "25" value(s) may not accurately reflect the sample, whereas excluding values above 24 will result in being underpowered for the other analysis.

Data collection: both the patient's electronic and paper charts will be accessed where applicable to obtain the necessary study data.

Gentamicin data collection

- Gentamicin data will be collected including: gentamicin dose, gentamicin start and stop dates/times, gentamicin infusion start and stop dates/times for the third dose, pre-third dose trough and post-third dose peak dates/times, and pre-third trough and post-third peak concentrations.

Safety parameter data collection

- Nephrotoxicity data including serum creatinine, BUN, and urine output (nephrotoxicity defined as: serum creatinine > 53 umol/L, BUN > 10 mmol/L, and urine output < 1 mL/kg/h)
- Ototoxicity measured by hearing test (pass/fail/no results available & date) which can be conducted in hospital, but are often completed in the outpatient setting.
- Safety data with corresponding dates will be collected for up to 7 days after discontinuation of gentamicin to follow trends in kidney tests. The first lab value for serum creatinine, BUN, and urine output will be recorded per day (in the case that multiple lab values are available).

Sample Size:

Participants will be recruited after gentamicin levels are documented. The needed sample size for Phase IV is n = 42 (n = 21 for < 35 weeks gestational age, n = 21 for at least 35 weeks gestational age). N = 42 will adequately detect a 0.5 mg/L difference in gentamicin concentrations with an 80% power, alpha of 5% and standard deviation of 0.5 mg/L. A

difference of 0.5 mg/L in gentamicin concentrations was selected to align with the initial phases of the study, while aligning with more recent evidence from a meta-analysis indicating a mean difference of 0.57 mg/L when comparing one dose per day to multiple doses per day of gentamicin dosed at 4-5 mg/kg/day in neonates (7).

Sample size calculations were conducted using the historical aggregate data from Phase I-III that included mean trough or peak gentamicin concentrations ± standard deviation, and proportion of gentamicin concentrations outside of target range. Each phase of historical data was compared to each other to estimate the needed sample size during Phase IV. The calculation comparing gentamicin troughs outside of target range between Phase I and Phase III ultimately guided the needed sample size as this calculation addressed the primary objective of achieving a larger of number of gentamicin troughs within target range, and Phase III matches the current regimen at our institution. This calculation resulted in n = 17 per group for gestational age < 35 weeks and n = 15 for at least 35 weeks. When comparing Phase I vs Phase III for mean gentamicin troughs, n = 12 per group for gestational age < 35 weeks and n = 5 per group for gestational age at least 35 weeks would be needed for 80% power with a 5% alpha. In order to be adequately powered to detect differences in gentamicin means and troughs, n = 21 per group was selected. This sample size also takes into account potential gentamicin level inaccuracies, and will help to minimize skewing of data from individual data points. Similarly, n = 21 per group allows for consistency in sample size when analyzing historical aggregate data to Phase IV.

Data Analysis:

SPSS version 30 (IBM Corp., Armonk, NY, USA) will be used for data analysis. Normally distributed continuous variables, including gentamicin concentrations, will be summarized with means and standard deviations (medians and interquartile ranges will be used for non-normal distributions). Forward extrapolation of trough and backward extrapolation of peak gentamicin concentrations will be performed to estimate the true trough and peak values by accounting for gentamicin timing and gentamicin blood draw inaccuracies.

The percentage of troughs and peaks within and outside of target range will be calculated and compared between the four phases of the study.

Independent t-tests with two-tailed p values will be conducted to detect differences in mean trough or peak gentamicin concentrations between the four phases of the study.

Chi-square tests will be conducted to detect differences in proportions (%) of troughs and peaks within and out of target range between the four phases of the study.

Subgroup analyses will be conducted to compare dosing in all phases of neonates < 35 weeks and all phases of neonates ≥ 35 weeks. If there are sufficient numbers, we may also assess dosing correlation with peak and trough concentrations in neonates < 28 weeks from phase III and IV.

Sawchuk-Zaske equations will be used for pharmacokinetic calculations, including elimination rate constant, volume of distribution, half-life, minimum concentration, and maximum concentration.

Application of Results & Future Implications

The current extended interval dosing regimen of gentamicin in neonates at the Children's Hospital at LHSC will be validated through this study. We will determine if current gentamicin dosing is reaching the target trough and peak values. The results will help determine if infants are receiving effective and safe treatment with gentamicin. Depending on the results of the study, further evaluation on changes to gentamicin dosing may be needed or an official guideline may be published if gentamicin levels are being adequately achieved with the current dosing. This official guideline will help prescribers at the Children's Hospital and hospitals in the surrounding region that will adopt our dosing when treating infants. There will be an overall benefit to prescribers and patients ensuring safe and effective of gentamicin dosing is followed.

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