Neonatal Serum Gentamicin Concentrations following Maternal Once-daily Gentamicin Dosing

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Background

- Gentamicin is commonly used in peripartum women for various obstetric-gynecologic infections, such as chorioamnionitis. It can be dosed as conventional three times a day (TIDD) or as a large once-daily dose (ODD) in pregnant mothers. Literature supports efficacy of ODD of 5 mg/kg for chorioamnionitis.[1-3]
- Gentamicin readily crosses the placenta and accumulates in fetal cord blood. Peripartum ODD dosing would be expected to lead to detectable levels in a neonate.
- Studies have shown significantly higher gentamicin serum concentration in cord blood from neonates born to mothers who received ODD versus TIDD.[1,4-6]
- Our institution implemented maternal ODD in October 2019. Due to the concern for elevated gentamicin serum concentrations after birth, a guideline was developed to measure newborn gentamicin concentrations with dosing adjusted based on level.

Objective

- To evaluate initial birth gentamicin serum concentrations and the effects on the newborn after ODD of gentamicin in peripartum mothers, including an evaluation of safety of our institutional guideline

Methods

- Design
  - Retrospective single center study
- Inclusion Criteria
  - Patients admitted to Neonatal Intensive Care Unit (NICU) from October 2019 – March 2020
  - Neonate's mother received peripartum ODD of gentamicin within 12 hours of delivery
  - STAT random gentamicin serum concentration obtained after birth (for primary outcome analysis)
- Exclusion Criteria
  - Neonates with mothers who received peripartum gentamicin > 12 hours prior to delivery
- Primary Outcome
  - Initial neonatal gentamicin serum concentration at birth
- Secondary Outcomes
  - Compliance with institutional guideline
- Sub-Group Analysis
  - Newborn birth gentamicin < 2 mcg/mL versus newborn birth gentamicin ≥ 2 mcg/mL
  - Outcomes:
    - Nephrotoxicity (↑ SCr ≥ 0.3 mg/L in first 7 DOL, UOP ≤ 0.5 mL/kg/hour on DOL 0, or UOP ≤ 1 mL/kg/hour on DOL 1 or 2)
    - Ototoxicity (final failed hearing screen)
    - Positive blood cultures
    - Time to clearance of blood cultures
    - Mortality

Results

Table 1: Baseline Characteristics

Characteristics	All subjects (n=32)	Newborn Birth Gent < 2 mcg/mL (n=11)	Newborn Birth Gent ≥ 2 mcg/mL (n=21)	p-value
Maternal Characteristics				
Age (years)	29.2 ± 5.6	30.7 ± 5.4	28.4 ± 5.7	0.271
Actual Body Weight (kg)	79 (69.5, 90.0)	82.6 (67.1, 136.3)	78.0 (70.7, 84.8)	0.592
Height (in)	63.4 ± 2.6	64.9 ± 2.1	62.6 ± 2.5	**0.010***
Serum Creatinine (mg/dL)	0.8 ± 0.3	0.6 ± 0.1	1 ± 0.3	**0.047***
Gentamicin Dose (mg/kg) – Actual Body Weight	4.6 (4.0, 5.1)	3.5 (3.3, 4.8)	4.8 (4.3, 5.2)	**0.025***
Positive Cultures	0 (0)	0 (0)	0 (0)	1.000
Time between gentamicin administration and delivery (hours)	1.8 (0.8, 3.3)	0.5 (0.3, 1.4)	2.6 (1.7, 3.4)	**0.005***
Neonatal Characteristics				
Gestational Age (weeks)	39.4 (37.4, 40.2)	39.1 (35.0, 40.3)	39.4 (38.6, 40.1)	0.842
Weight (kg)	3.4 (3.0, 3.7)	3.7 (2.9, 3.9)	3.4 (3.0, 3.7)	0.525
Sex (Male)	20 (62.5)	7 (63.6)	13 (61.9)	1.000
Time between delivery and serum gentamicin concentration (minutes)	43 (37, 64.5)	43 (36, 80)	43 (37, 64)	0.781
Other ototoxic medications during admission	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Other nephrotoxic medications during admission	1 (3.1)	1 (9.1)	0 (0)	0.344

All data is presented as n (%), median (IQR), or mean ± SD
*Statistically significant

Table 3: Neonatal gentamicin dosing algorithm

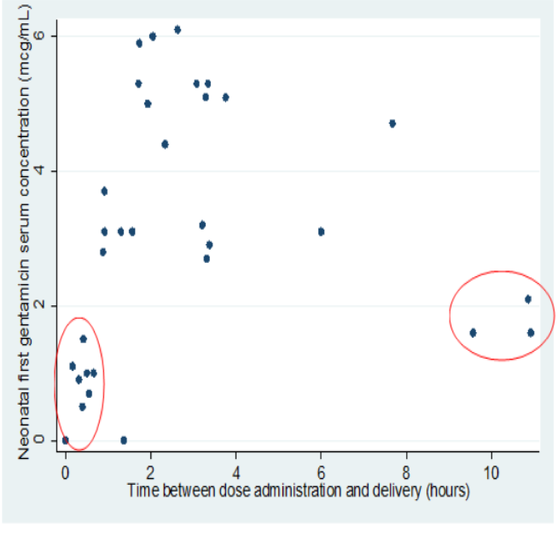
Gentamicin serum concentration	Birth weight < 2 kg	Birth weight ≥ 2 kg
≥ 6 mcg/mL	36 hours after level, start gentamicin	24 hours after level, start gentamicin
4 to < 6 mcg/mL	24 hours after level, start gentamicin	12 hours after level, start gentamicin
2 to < 4 mcg/mL	12 hours after level, start gentamicin	6 hours after level, start gentamicin
< 2 mcg/mL	NOW, start gentamicin	NOW, start gentamicin
DOSE	4 mg/kg every 36 hours	4 mg/kg every 24 hours

Table 2: Newborn Outcomes

Outcomes	All subjects (n=32)	Newborn Birth Gent < 2 mcg/mL (n=11)	Newborn Birth Gent ≥ 2 mcg/mL (n=21)	p-value
Initial serum gentamicin concentration (mcg/mL)	3.1 ± 1.9	0.9 ± 0.6	4.2 ± 1.3	**< 0.0001***
Initial gent course (days)	2 (2, 3)	3 (2, 3)	2 (2,2)	0.069
Compliance to Protocol	26 (81.3)	9 (81.8)	17 (81.0)	1.000
Failed initial hearing screen	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Failed repeat hearing screen	1 (3.1)	0 (0)	1 (4.8)	1.000
Nephrotoxicity • ↑SCr • Low UOP	5 (15.6) 2 (6.3) 3 (9.3)	2 (18.2) 1 (9.1) 1 (9.1)	3 (14.3) 1 (4.8) 2 (9.5)	1.000
Maximum SCr in first 7 DOL	0.9 (0.7, 0.9)	0.85 (0.6, 0.9)	0.9 (0.7, 0.9)	0.756
Positive blood culture within the first 72 HOL	1 (3.1)	0 (0)	1 (4.8)	1.000
14-Day Mortality	0 (0)	0 (0)	0 (0)	1.000

All data is presented as n(%), median (IQR), or mean ± SD
*Statistically significant

Figure 1: Comparison of maternal gentamicin time from administration to delivery and neonatal serum gentamicin concentrations



Results

One patient with positive blood culture after birth

- Blood culture: + *Escherichia coli*
  - Ampicillin – resistant
  - Gentamicin – susceptible
- Maternal dose given 3.3 hours prior to delivery
- Initial neonatal serum concentration: 2.7 mcg/mL
- First gentamicin dose was held per guideline for 12 hours based on initial gentamicin level
- Cleared blood culture in 24 hours
- Transitioned to cefotaxime on day 3 of therapy
- Gentamicin pharmacokinetic levels at steady state:
  - Peak 8.5 mcg/mL, trough 0.76 mcg/mL, Half-life 10.2 hours, Ke 0.068, Vd 0.5 L/kg
- Failed repeat hearing screening in both ears prior to discharge
- No other potentially nephrotoxic or ototoxic medications were administered

Conclusions

- Gentamicin ODD of 5 mg/kg administered between 1 and 12 hours prior to delivery leads to clinically elevated serum concentrations in neonates.
- Neonates who were born within 1 hour of peripartum gentamicin administration did not have supratherapeutic levels based on this analysis.
- No safety concerns related to ototoxicity or nephrotoxicity were identified.
- A neonate with an initial gentamicin trough ≥ 2 mcg/mL who had their initial dose of gentamicin delayed by 12 hours per protocol cleared *E. coli* blood cultures within 24 hours, which supports the safety of our institutional dosing strategy.
- Further studies are warranted to evaluate the effects of maternal ODD of gentamicin on newborns and the optimal therapeutic monitoring strategy.

Limitations

- Small sample size
- Single center
- Limited long-term follow up
- Limited therapeutic drug monitoring

References

1. Locksmith GJ, Chin A, Vu T, et al. *Obstet Gynecol* 2005;105:473–9.
2. Ward K, Theiler RN. *Clin Obstet Gynecol*. 2008; 51(3): 498–506.
3. Lyell DJ, Pullen K, Fuh K, et al. *Obstet Gynecol* 2010;115:344–9.
4. Yoshioka H, Monma T, Matsuda S. *J Pediatr* 1972;80:121–3.
5. Daubenfeld O, Modde H, Hirsch H. *Arch Gynecol* 1974;217:233–40.
6. Regev RH, Litmanowitz I, Arnon S, et al. *Pediatr Infect Dis J* 2000;19:890–1.

Disclosures

The authors of this presentation have no financial interests with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.