A Pharmacokinetic Assessment of Extended-Interval Aminoglycoside Dosing in Neonates

Mattie Bakker, B.Sc.(Pharm); Vanessa Paquette, B.Sc.(Pharm), ACPR, Pharm.D; Jason Tan, B.Sc.(Pharm), ACPR, Pharm.D; Roxane Carr, B.Sc.(Pharm), ACPR, Pharm.D, BCPS, FCSHP

Background

- Extended-interval dosing of aminoglycosides (EIA) involves the use of higher doses with longer intervals between doses
- In neonates, EIA is used to take advantage of the reduced clearance and increased volume of distribution (V_d) to achieve the same target serum concentrations as traditional dose aminoglycosides (TDA)
  - Target peak: 5 – 12 mg/L; Target trough: < 2 mg/L
- EIA has been minimally studied in premature neonates, particularly in those born at < 32 weeks gestational age (GA)
- The BC Women's Hospital Neonatal Intensive Care Unit (BCWH NICU) replaced the TDA protocol with an EIA protocol in June 2017:

Age 0-7 Days (Use GA)		Age > 8 Days (Use PCA*)	
GA (weeks)	**Dose**	**PCA* (weeks)**	**Dose**
< 30	5 mg/kg IV x 1	< 30	5 mg/kg IV x 1
30 – 34	4 mg/kg IV Q36H	≥ 30	4 mg/kg IV Q24H
≥ 35	4 mg/kg IV Q24H		

*PCA = postconceptional age = GA [weeks] + postnatal age (PNA) [weeks]

Objectives

Primary: To determine if EIA is noninferior to TDA at achieving target serum concentrations

Secondary:
- Compare between the EIA and TDA groups:
  - Number of serum concentrations measured
  - Proportion of patients requiring dose adjustment
  - Adverse effects
- Describe the pharmacokinetic parameters of gentamicin in neonates

Methods

Design: Retrospective, noninferiority, pre-post, observational cohort study
- Patients stratified into five groups based on GA and PNA, to a maximum of 25 patients per strata

Inclusion: Neonates admitted to the BCWH NICU who received ≥ 1 dose of gentamicin and had ≥ 1 gentamicin serum concentration measured

Exclusion: Single gentamicin serum concentration measured outside the time frame to be a peak or trough

Adverse Effects: Naranjo score ≥ 1 included
- Acute kidney injury (AKI): urine output ≤ 1 mL/kg/h for ≥ 24 hours, or serum creatinine rise ≥ 26 µmol/L or ≥ 1.5 x baseline during gentamicin treatment
- Ototoxicity: failed hearing screen

Statistics: Chi-squared; Fisher's exact; Student's t

Sample Size: N = 150; noninferiority limit 5% for the primary outcome

Results

Table 1: Patient Characteristics

	TDA (N=75)	EIA (N=75)
GA (wk) – median (range)	31 (23 – 42)	32 (23 – 41)
GA ≤ 32 wk – n (%)	44 (59)	49 (65)
PNA (d) – median (range)	0 (0 – 80)	0 (0 – 90)
Weight (kg) – median (range)	1.8 (0.5 – 4.5)	1.8 (0.5 – 4.4)
Duration of gentamicin (d) – mean (SD)	5.1 (2.4)	5.2 (2.1)
Nephrotoxic Medications – n (%)		
Furosemide	11 (15)	7 (9)
Nonsteroidal anti-inflammatory	8 (11)	6 (8)
Vancomycin	1 (1)	3 (4)
Acyclovir	3 (4)	4 (5)
Medical Conditions – n (%)		
Patent ductus arteriosus	7 (9)	9 (12)
Hypoxic ischemic encephalopathy	0 (0)	3 (4)
Positive blood cultures – n (%)	5 (7)	5 (7)

Figure 1: Patients Achieving Target Serum Concentrations

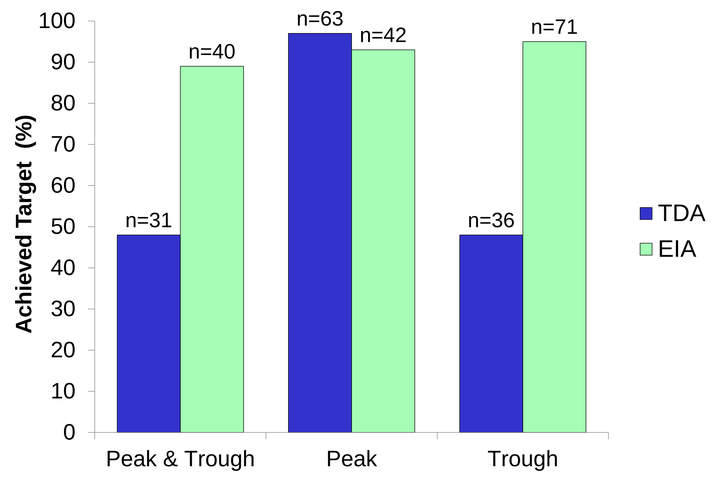

Figure 2: Difference in Achievement of Target Serum Concentrations

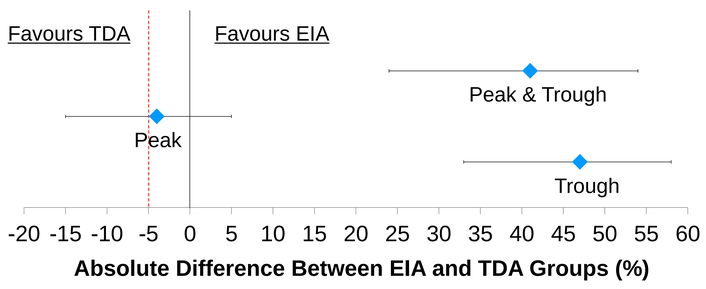

Table 2: Secondary Outcomes

	TDA (N=75)	EIA (N=75)	p-Value
Patients with ≥ 1 peak measured – n (%)	65 (87)	45 (60)	-
Patients with ≥ 1 trough measured – n (%)	75 (100)	75 (100)	-
Patients with peak & trough measured – n (%)	65 (87)	45 (60)	-
Number of serum concentrations measured per patient – mean (SD)	2.0 (0.6)	1.7 (0.7)	0.006
Patients requiring dose adjustment – n (%)	39 (52)	10 (13)	< 0.001

Figure 3: Peak & Trough Serum Concentrations

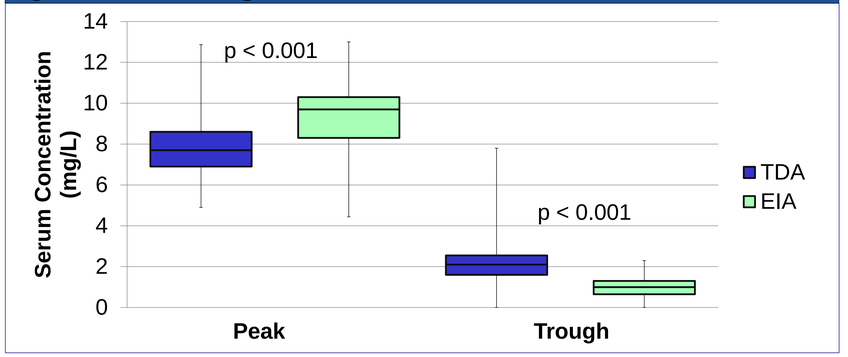

Table 3: Pharmacokinetic Parameters

	TDA (N=65)	EIA (N=45)
K (h^{-1}) – median (range)	0.1 (0.03 – 0.3)	0.09 (0.04 – 0.2)
Half-life (h) – median (range)	6.8 (2.5 – 26.5)	7.8 (4.4 – 15.7)
V_d (L/kg) – median (range)	0.4 (0.2 – 1.3)	0.4 (0.3 – 1.2)

Table 4: Safety Outcomes

	TDA (N=75)	EIA (N=75)	p-Value
AKI – n (%)	1 (1)	3 (4)	0.62
Ototoxicity – n (%)	4 (5)	7 (9)	0.52
Mortality – n (%)	3 (4)	5 (7)	0.49

Limitations

- Not all patients had a peak and trough serum concentration measured
- Unable to assess clinical effectiveness

Conclusions

- EIA is noninferior to TDA at achieving target serum concentrations in neonates
- EIA is superior to TDA at achieving target serum concentrations in neonates
- Education is required among NICU staff regarding the importance of measuring both peak and trough serum concentrations for aminoglycoside monitoring
- Further studies are needed to assess clinical effectiveness and safety