A Pharmacokinetic Validation Study of Once Daily Dosing of Intravenous Gentamicin and Tobramycin in Paediatric Patients

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Background

- **Aminoglycosides**, such as gentamicin and tobramycin, are commonly used antibiotics against serious gram-negative bacterial infections.
- Potential benefits of once daily dosing (ODD) aminoglycosides based on their pharmacokinetic and pharmacodynamic properties are: **concentration-dependent effect, post-antibiotic effect, and decrease risk of adaptive resistance, nephrotoxicity and ototoxicity.**
- **Experience at the Hospital for Sick Children (SickKids):**
  - In-house pharmacokinetic studies have led to implementation of ODD aminoglycosides in the following subpopulations: haematology/oncology (Haem/Onc), haematopoietic stem cell transplant (HSCT), cystic fibrosis, and critically ill patients.
  - In July 2014, based on dose-validation study in critically ill patients, ODD aminoglycosides was implemented to all SickKids inpatients.

Objectives

- **Primary Objectives:**

To validate the implemented gentamicin or tobramycin dose of **9 mg/kg every 24 hours** in eligible paediatric inpatients.

  - *Endpoints:* Calculated C_{max}, % of patients attaining target C_{max} of 16-25 mg/L, and final dose of gentamicin or tobramycin after Therapeutic Drug Monitoring (TDM) needed to achieve target C_{max}.

- **Secondary Objectives:**

1. To determine the **efficacy and safety** of ODD of gentamicin and tobramycin.
   - *Efficacy Endpoints:* clinical cure (changes in WBC count, time to defervescence), and eradication of organisms based on microbiology results
   - *Safety Endpoints:* nephrotoxicity (changes in urine output, serum creatinine, blood urinary nitrogen), and ototoxicity (audiometry testing if therapy is longer than 14 days)
2. To determine **patient characteristics** that may affect pharmacokinetic parameters [C_{max}, area under the concentration-time curve (AUC), drug free interval (DFI)] of gentamicin or tobramycin.

Methods

Study design	Retrospective, single-centre cohort
Intervention	Gentamicin or tobramycin 9 mg/kg/dose IV q24h
Study sample	***Inclusion criteria:*** Inpatients given ODD of gentamicin or tobramycin empirically, for documented infection with gram negative organisms, or for prophylaxis. ***Exclusion criteria:*** • Weight ≤ 5 kg • Renal failure • Kidney, lung and/or small bowel transplant • Endocarditis or other gram positive infections • Cystic fibrosis • Newborn infants • Haem/Onc, HSCT, severe combined immunodeficiency • Known prior allergy to aminoglycosides • Hearing impairment or family history of aminoglycoside-induced hearing loss
Sample size	153 (convenient sample size; from July 2, 2014 to December 31, 2014)
Ethics	Approved by the Research Ethics Board
Data Sources	Pharmacy records, electronic patient charts, KidCare, Clinical Information Management System

Statistical analysis

Pharmacokinetic calculations based on one-compartmental model (Sawchuk-Zaske method)

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Descriptive statistics to summarize study endpoints

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Monte Carlo simulations with Oracle Crystal Ball®

Results

Table 1. Patient Demographics

Characteristics	All patients
Number of patients	147
Number of courses	153
Unit Admitted, n (%)	
Cardiac Critical Care Unit (CCCU)	9 (5.88)
Cardiology	5 (3.27)
Gastroenterology, Hepatology and Nutrition / Nephrology	3 (1.96)
General Paediatrics	21 (13.73)
Neurology	1 (0.65)
Paediatric Intensive Care Unit (PICU)	17 (11.11)
Surgery	97 (63.40)
Male, n (%)	81 (55.10)
Age, [a] mean (SD) in years	7.05 (5.33)
Weight, [a] mean (SD) in kg	25.51 (19.38)
Drug received	
Tobramycin, n (%)	147 (96.08)
Gentamicin, [b] n (%)	6 (3.92)
Indication for therapy, n (%)	
Empiric	109 (71.24)
Documented	36 (23.53)
Prophylaxis	8 (5.23)
Pathogens isolated, [c] n (%)	42 (23.52)
Acinetobacter spp.	1 (2.38)
Enterobacter clacae	4 (9.52)
Escherichia coli	10 (23.81)
Klebsiella oxytoca	6 (14.29)
Klebsiella pneumonia	3 (7.14)
Pseudomonas aeruginosa	10 (23.81)
Serratia marcescens	1 (2.38)
Sphingomonas paucimobilis	1 (2.38)
Stenotrophomonas maltophilia	3 (7.14)
Gram negative (no organism specified)	3 (7.14)

[a] At start of therapy, [b] Gentamicin is on backorder from July 2014, [c] Two different gram negative bacteria were isolated from four patients. SD, standard deviation.

Table 2. Pharmacokinetic parameters after first aminoglycoside dose

Parameter	All patients (n=115)	Non-critically ill patients (n=93)	Critically ill patients (n=22)
Gentamicin or tobramycin dose (mg/kg)	8.95 (0.44)	8.96 (0.46)	8.89 (0.28)
Duration of therapy (days)	3.49 (2.70)	3.41 (2.64)	3.83 (2.99)
K_e (h^{-1})	0.35 (0.07)	0.36 (0.06)	0.29 (0.07)
V_d (L/kg)	0.51 (0.28)	0.52 (0.29)	0.46 (0.25)
Cl (L/h/kg)	0.17 (0.08)	0.18 (0.07)	0.13 (0.09)
C_{max} (mg/L)	18.65 (7.78)	17.82 (7.27)	22.14 (9.01)
AUC (mg*h/L)	65.27 (33.13)	58.71 (23.47)	93.02 (9.01)
DFI (h)	17.00 (2.25)	17.52 (1.43)	14.78 (3.50)
C_{max} target 16-25 mg/L:			
Subtherapeutic, n (%)	47 (40.87)	42 (45.16)	5 (22.73)
Within target range, n (%)	51 (44.35)	40 (43.01)	11 (50.00)
Supratherapeutic, n (%)	17 (14.78)	11 (11.83)	6 (27.27)

Reported as mean and standard deviation. Critically ill patients defined as patients admitted to CCCU or PICU. Non-critically ill patients defined as patients admitted to inpatient units other than CCCU or PICU.
AUC, area under the concentration-time curve; Cl, clearance; C_{max}, maximum serum concentration; DFI, drug free interval; k_e, elimination constant; V_d, volume of distribution.

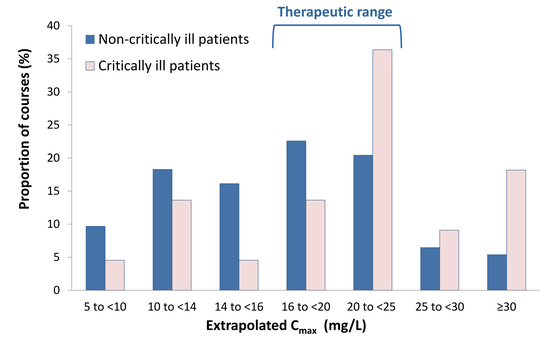

Figure 1. Distribution of proportion of courses for C_{max} achieved using 9 mg/kg IV every 24 hours

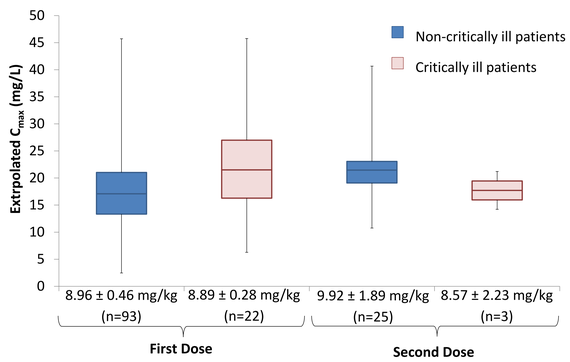

Figure 2. C_{max} attainment with dose adjustments

Table 3. C_{max} target attainment predicted by Monte Carlo simulations using 10^6 trials

Simulated Dose (mg/kg)	8	9	9.5	10	11	12
Proportion of simulated patients [a] attaining C_{max}	31.82	33.52	33.78	33.72	32.72	31.08

[a] Based on simulation trials using pharmacokinetic parameters derived from the study sample.

Table 4. Target C_{max} attainment with first dose and volume of distribution differences by post-operative day

	No surgery (n=32)	Postop Day 0 (n=14)	Postop Day 1 (n=23)	Postop Day 2 (n=7)	Postop Day 3 (n=4)	Postop Day >3 (n=13)
% of courses attaining C_{max} target	43.75	50.00	39.13	42.86	25.00	46.15
V_d, mean (SD) (L/kg)	0.56 (0.41)	0.41 (0.10)	0.54 (0.22)	0.48 (0.17)	0.64 (0.37)	0.44 (0.14)

C_{max}, maximum serum concentration; Postop, post-operative; V_d, volume of distribution.

Table 5. Efficacy and Safety Parameters

Parameter	All patients
Eradication of organism, n (%)	10/14 (71.42)
Resistance to tobramycin (either resistant or intermediate), n (%)	4/36 (11.11)
Resistance to gentamicin (either resistant or intermediate), n (%)	3/36 (8.33)
Percent change of white blood cell count, [a] %	-16.46 (-37.32 to 9.41)
Defervescence, n (%)	88/95 (92.63)
Percent change of serum creatinine, [a] %	5.84 (-10.96 to 19.18)
Percent change blood urea nitrogen, [a] %	2.27 (-28.57 to 73.03)
Percent change of urine output, [a] %	-13.37 (-42.02 to 24.51)
Concomitant nephrotoxic agents, n (%)	31 (20.26)
Acyclovir	1 (0.65)
Amphotericin	2 (1.31)
Furosemide	22 (14.38)
Vancomycin	17 (11.11)

[a] Reported as median and interquartile ranges

Discussion

Pharmacokinetic Dose Validation:

- Over 44% of courses achieved therapeutic C_{max} target range. Of those courses that did not reach C_{max} target range, half of the extrapolated C_{max} were accepted due to either: 1) C_{max} being within 2 mg/L away from target range, 2) patients clinically well without documented infection or 3) course duration ended within the next 24 hours.
- The mean volume of distribution of the study sample was greater than what was reported in the literature (0.3-0.4 L/kg) possibly due to a majority of included patients were admitted under surgery and received bolus fluids pre- and post-operatively.
- C_{max} target attainment was superior in critically ill patients than non-critically ill patients, suggesting that a higher dose may be required for non-critically ill patients.
- Using existing study sample pharmacokinetic parameters, a proposed daily dose of 10 mg/kg may resulted in a small increase in target C_{max} attainment in non-critically ill patients. However, the Monte Carlo simulation accounting for study sample variability demonstrated minimal changes in achieving target C_{max} range with simulated doses from 8-12 mg/kg/dose.
- In the subgroup analysis of surgical patients, significant increases in calculated volume of distribution occurred at first dose of therapy likely due to bolus fluids given pre- and post-operatively. Therefore, considerations should be given to delay sampling time for aminoglycosides to post-op Day 2 or 3 in patients who are not clinically deteriorating and being treated empirically or prophylactically.

Efficacy:

- Almost all patients defervesced, and in those with repeated cultures, majority showed eradication of organism. WBC trended down.

Safety:

- There was significant variability in renal function. In patients who had elevated serum creatinine and BUN levels, majority were receiving concomitant nephrotoxic drugs. ODD aminoglycosides did not seem to be associated with significant changes in renal markers.
- Majority of courses were shorter than 14 days and for the patient who had audiometry testing, no ototoxic effects were identified.

Limitations:

- Retrospective study with incomplete data.
- Majority of patients were admitted under surgery, which may limit the study findings' generalizability to non-surgical paediatric patients.
- C_{max} target was based on MIC of 2 mg/L for *Pseudomonas aeruginosa* reported at SickKids' Microbiology lab and may not apply to all gram negative organisms.
- A small sample size for analyzing secondary outcomes, i.e. safety of drugs, treatment success, and C_{max} attainment by post-operative day.

Conclusion

- Study validated that the initial gentamicin or tobramycin dose of 9 mg/kg IV every 24 hours is able to achieve a therapeutic target C_{max} range of 16-25 mg/L.
- Therapeutic drug monitoring guidelines will be revised to address:
  - Patients who may need two-point sampling for pharmacokinetic parameters calculation
  - Patients who may only require one-point sampling to ensure adequate drug clearance
  - Optimal TDM sampling days in post-operative patients on days
- Future directions include knowledge translating practice of ODD gentamicin and tobramycin to inpatients at other paediatric hospitals.

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