Aminoglycoside Pharmacokinetics and Optimal Once Daily Dosing in Burn Patients: A Prospective Study

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Underwritten by: Master of Science Candidate working under supervision of Sandra Walker at time of study; "Senior Author" sequence determines credit to authors

BACKGROUND

• Adequate dosing of aminoglycosides in burn injury patients is challenging due to the physiologic changes associated with burn injury that affect the pharmacokinetics of antibiotics.

• Burn injury patients are at increased risk of infection due to the breach in the natural skin barrier and concomitant suppression of both the cellular and innate immune system.

• Burn wound-induced edema is a major cause of mortality and morbidity in burn patients, and Pseudomonas aeruginosa is commonly pathogenic.

• All the Ross Tilley burn centre, Ontario’s largest burn unit, Pseudomonas aeruginosa susceptibility was found to be highest with tobramycin.

• Appropriate empiric aminoglycoside dosing in burn injury patients is essential to maximize the probability of achieving early pharmacodynamic/pharmacokinetic targets to optimize antibacterial activity and successful clinical outcome.

RATIONAL

• Once daily aminoglycoside (ODA) dosing is an attractive dosing modality because it optimizes the concentration-dependent bactericidal activity of aminoglycosides, while potentially limiting nephrotoxicity. Unfortunately, this dosing regimen is not recommended for burn patients due to concerns of sub-optimal levels and prolonged drug-free intervals arising from the changes in aminoglycoside pharmacokinetics in this population.

• Despite the recognized need for prospective study, the available literature is limited. This study was undertaken to determine the ability of a single tobramycin 10 mg/kg dose to achieve target extrapolated maximum (Cmax) and minimum (Cmin) concentrations in burn patients with less than 20% total body surface area (TBSA).

OBJECTIVES

• Evaluate the pharmacokinetic findings from our previously published work using a retrospective prospective study design.

• Characterize (i) baseline parameters, (ii) distribution of MICs, (iii) area-under-curve (AUC), (iv) half-life (T1/2).

• Prospectively determine the ability of a single tobramycin 10 mg/kg dose to achieve target extrapolated maximum (Cmax) and minimum (Cmin) concentrations in burn patients with less than 20% TBSA.

• Determine the optimal aminoglycoside dosing to achieve the highest probability of obtaining target concentrations while minimizing the risk of toxicity using Monte Carlo simulation (MCS).

METHODS

**Study Design**

Health Canada approved prospective, non-randomized, unblinded clinical trial (ClinicalTrials.gov NCT02269969)

**Study Setting**

Ross Tilley Burn Unit at Sunnybrook Health Sciences Centre, Toronto, Canada

Ontario’s largest burn unit with 11 adult beds servicing the Greater Toronto area and all of the province

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tr>
<td>- Adult burn patient (≥ 18 years)</td>
<td>- Active liver and/ or renal failure</td>
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<tr>
<td>- TBSA: Surface area (TBSA) ≤ 20%</td>
<td>- History of nephrotoxicity</td>
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<td>- At least 48 hours after the time of initial burn event</td>
<td>- Known allergy to aminoglycosides</td>
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<tr>
<td>- Had been receiving antibiotic therapy for at least 24 hours</td>
<td>- Known allergy to aminoglycosides</td>
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<tr>
<td>- Documented history of coexisting or potential wound infection</td>
<td>- Known allergy to aminoglycosides</td>
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<tr>
<td>- Creatinine clearance ≥ 50 mL/min</td>
<td>- Known allergy to aminoglycosides</td>
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<tr>
<td>- Requiring any modality of dialysis</td>
<td>- Known allergy to aminoglycosides</td>
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<tr>
<td>- No history of alcohol abuse or use of medications known to affect aminoglycosides</td>
<td>- Known allergy to aminoglycosides</td>
</tr>
<tr>
<td>- Known diagnosis of Parkinson’s disease or nephrotoxic greasy</td>
<td>- Known allergy to aminoglycosides</td>
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**Analysis**

- One or two compartment two stage analysis to determine PK parameters (Vd, Cl, T1/2).
- Univariate and multiple variable regression to determine covariates of Vd and Cl.
- MCS to evaluate the probability of obtaining target maximum concentration (Cmax) ≤ 20 mg/L and peak to MIC ratio of >10 in burn patients.
- Aminoglycoside Pharmacokinetics and Optimal Once Daily Dosing in Burn Patients: A Prospective Study

**Intervention**

- Aminoglycoside trough sampling (i.e. c. 12 hours post dose) dosing weight of aminoglycosides, and peak and trough levels from the 7 patients that achieved target Cmax.
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- Aminoglycoside trough sampling (i.e. c. 12 hours post dose) dosing weight of aminoglycosides, and peak and trough levels from the 7 patients that achieved target Cmax.

- MCS: to estimate the probability of obtaining target maximum concentration (Cmax) of > 20 mg/L and peak to MIC ratio of >10 in burn patients.

**RESULTS**

**Objectives**

**Methodology**

**Results**

**Discussion**

**Conclusion**

**Future work**

- MCS: to estimate the probability of obtaining target maximum concentration (Cmax) of > 20 mg/L and peak to MIC ratio of >10 in burn patients.

- Larger sample size can improve the confidence of this study.

- Exposed population to include TBSA > 20%. Further examination of target extrapolated maximum (Cmax) and minimum (Cmin) concentrations will be required.

- Clinical trial of once daily aminoglycoside dosing in the burn population.