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A prospective study evaluating tobramycin pharmacokinetics and optimal once daily dosing in burn patients☆

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ABSTRACT

Background: Once-daily aminoglycoside dosing (ODA) is used in most patient populations to optimize antibacterial activity and reduce toxicity. Unfortunately, burn patients are excluded from ODA due to concerns over altered pharmacokinetics resulting in a shortened half-life and low peak aminoglycoside concentrations. Retrospective studies suggest that ODA may be appropriate if higher milligram/kilogram doses are used. However, no prospective clinical trials in burn patients exist to confirm these findings.

Objective: To determine the adequacy of once daily tobramycin dosed at 10mg/kg in adult burn patients.

Methods: This prospective single dose pharmacokinetic clinical trial was conducted at the Ross Tilley Burn Centre. Patients with a total burn surface area (TBSA) of <20% and creatinine clearance ≥50mL/min were eligible. A first-order one compartment model was used to determine the pharmacokinetic profile from 3 or 5 tobramycin levels over a 24h period per patient. Monte Carlo simulation (MCS) was performed to determine the probability of target level attainment.

Results: The mean percent TBSA, partial, and full thickness burn were 10%, 6%, and 4%, respectively. Nine of the ten patients recruited achieved peak concentrations of ≥20mg/L (mean of 29.4±5.7mg/L) and all patients had a trough level ≤0.5mg/L. The mean half-life,

Abbreviations: Cmax, extrapolated maximum concentration immediately after the end of the infusion; Cmin, extrapolated minimum concentration immediately after the end of the infusion; Cl, clearance (L/h); CrCl, creatinine clearance; GFR, glomerular filtration rate; T1/2, half-life; k, elimination rate constant; MCS, Monte Carlo simulation; MIC, minimum inhibitory concentration; ODA, once daily aminoglycosides; RTBC, Ross Tilley Burn Centre; SHSC, Sunnybrook Health Sciences Centre; TBSA, total burn surface area; Vd, volume of distribution.

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volume of distribution, and clearance were 2.58 h, 0.33 L/kg, and 7.40 L/h, respectively. The MCS determined probability of attaining target peak concentrations with the 10 mg/kg dose was 97%, which almost doubled that predicted with the usual 7 mg/kg dose.
Conclusion: Burn patients with adequate renal function and <20% TBSA are candidates for ODA. Tobramycin half-life was similar to healthy, non-burn patients. The larger than normal volume of distribution supports the use of the higher empiric dose of 10 mg/kg total body or adjusted weight in non-obese and obese patients, respectively, with further dose adjustment based on therapeutic drug monitoring.

1. Introduction

Infection is an important and potentially serious complication for burn patients [1,2]. Among the pathogens that may cause infection, *Pseudomonas aeruginosa* is commonly identified in burn wound and ventilator-associated infections in the weeks following burn [1,3–6]. Given this pathogen's propensity for antimicrobial resistance [7–12], burn patients may benefit from an aminoglycoside for the treatment of an infection if resistance exists to other anti-pseudomonal antibiotics. Unfortunately, significant changes in physiology can occur after a patient sustains a burn [3,13,14], which can have great impact on aminoglycoside pharmacokinetics. Notably, the hypermetabolic phase that occurs greater than 48 h after the initial burn is characterized by increased metabolism, increased cardiac output, and low systemic vascular resistance, which can lead to an increase in aminoglycoside elimination and volume of distribution (Vd) [15–17].

The once daily aminoglycoside (ODA) dosing regimen is commonly used in many non-burn patient populations due to its ability to optimize aminoglycoside bactericidal activity by achieving a desirable peak concentration to minimum inhibitory concentration (MIC) ratio of 8 to 10, and potentially reducing the risk of nephrotoxicity [18–20]. Despite the common use of the ODA dosing regimen in clinical practice, this regimen is not typically used in the burn population due to concerns about the potential risk for inadequate serum concentrations and prolonged drug-free intervals leading to decreased efficacy [18,21] as a result of the changes in drug pharmacokinetics. Although the changes in aminoglycoside pharmacokinetics after a burn are a concern, prospective clinical trials investigating the use of the ODA regimen are lacking, and so burn patients may potentially be unnecessarily deprived of the benefits from an ODA regimen when being treated with an aminoglycoside for infection. Despite a number of more recent studies [22–25] examining the potential use of the ODA regimen in burn patients, results have generally been inconclusive because of variability in the study patient population and ODA dose evaluated. These studies also evaluated the use of the ODA regimen using retrospective data and dosing simulation, and so the results still require clinical validation. Conil et al. prospectively validated the use of once daily amikacin and found an overall increase in drug Vd and clearance (Cl), similar to previous studies, but did not find a significant difference in half-life (T1/2) compared to non-burn patients [24]. The results validated a need for a higher milligram per kilogram (mg/kg) dose of aminoglycosides in burn patients. Unfortunately, the dosing recommendation for amikacin is not applicable to other commonly used aminoglycosides, such as tobramycin or gentamicin, and so the optimal dosing regimen for these aminoglycosides remains unclear in the burn population.

Existing literature supports the possibility for ODA dosing in burn patients, but requires further clinical validation to determine the true utility and empiric dosing, especially for tobramycin and gentamicin. Based on our prior work simulating a variety of once daily tobramycin doses, it was found that a fixed initial ODA dose of 10 mg/kg would result in a high probability of achieving target drug concentrations in the burn population [25]. The research hypothesis of this study was that once daily dosing of tobramycin at 10 mg/kg total body weight would provide targeted peak concentrations of ≥20 mg/L and 24 h extrapolated trough concentrations ≤0.5 mg/L, thereby supporting the clinical utility of ODA in burn patients. The objective of this study was to prospectively validate the ability of an initial empiric once-daily tobramycin dose of 10 mg/kg to attain desired serum concentrations in burn patients, thereby supporting the use of a dosing modality that has been associated with optimal outcome and safety in other patient populations. Additional objectives for this study were to determine the risk of nephrotoxicity with this dosing regimen, and to further evaluate the pharmacokinetics of tobramycin in burn patients.

2. Methods

2.1. Study population

This prospective, non-randomized, clinical pharmacokinetic study was conducted in the Ross Tilley Burn Centre (RTBC) at Sunnybrook Health Sciences Centre (SHSC), a tertiary care teaching hospital in Toronto, Ontario, Canada. The Research Ethics Board at SHSC granted approval for this study on October 9, 2014, and Health Canada Clinical Trial Application (CTA) approval was received on October 7, 2014. This study was also registered with ClinicalTrials.gov (NCT02269969).

The RTBC is an American Burn Association and American College of Surgeons verified burn center with a 14 bed capacity to provide care for adult burn patients living in the Greater Toronto Area and other parts of Ontario. The RTBC has approximately 200 burn admissions annually where patients with <20% total burn surface area (TBSA) make up about 80% of burn patients admitted to the center [26]. Inclusion criteria for this study were the following: adult patients (18 years or older),

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