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Suboptimal Aminoglycoside Dosing in Critically Ill Patients

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Introduction/Purpose: Maximal aminoglycoside (AG) killing requires that peak serum concentrations (C_{max}) exceed the minimum inhibitory concentration (MIC) of the pathogen by ≥ 10 (C_{max}/MIC). Achievement of this target with gentamicin or tobramycin (5 to 7 mg/Kg) has been shown to hasten resolution of infection in the general patient population. It was postulated that critically ill patients, likely to have larger intravascular volumes because of over-hydration, are under-dosed such that unconventionally high AG doses would be required to attain the C_{max}/MIC target. Our primary aim was to determine the C_{max}/MIC target attainment rate in medical ICU patients.

Methods: A retrospective review of medical ICU patients who received at least one IV dose and serum concentration of either gentamicin or tobramicin from January 1, 2001 to December 31, 2004 was performed. Patients with cystic fibrosis, organ transplantation, those receiving dialysis, or those receiving doses <3 mg/Kg were excluded. Patient demographics and amount and timing of aminoglycoside doses and levels were collected. Population pharmacokinetic (PK) parameters (C_{max}, CL, V) were estimated using an open-linear one-compartment model (NONMEM, Version V, University of California, San Francisco). Mean inhibitory concentration (MIC) distributions of gentamicin and tobramycin for all UPMC ICUs from 1/1/2001 to 12/31/2004 were used in determining the C_{max}/MIC and in calculating the probability of attaining the pharmacodynamic (PD) target.

Results: One-hundred two unique patients with 211 AG concentrations were analyzed to determine population PK parameters. Mean maximum clearance (CL) was 3.14L/hr (95% CI 1.26-4.54). The mean volume of distribution (V) was 53 L (95% CI 38-66.8). Glomerular filtration rate and standardized body weight were identified as significant covariates for CL and V, respectively in the final model. For pathogens with an MIC of 1 μg/mL, only 50% of patients receiving a dose of 7 mg/Kg will achieve PD targets and this rate decreases to only 10% of patients as the MIC increases to 2 μg/mL. When the range of MIC distributions were taken into account, there was only a 20% and 40% probability that patients receiving 7 mg/Kg of gentamicin and tobramycin, respectively will achieve the PD target of C_{max}/MIC greater than or equal to 10.

Conclusions: The majority of these critically ill patients did not achieve a PD goal of Cmax/MIC ≥ 10, especially with an MIC of 2 μg/mL. Explanations include a larger volume of distribution for

ICU patients than reported in the literature. Future recommendations for treating Gram-negative infections in the medical ICU population include utilizing initial doses of 7 mg/Kg of either gentamicin or tobramycin, checking C_{max} after the first dose, and determining MIC for the pathogen(s) with adjustment of subsequent doses to achieve the PD target. Future prospective analysis studying effects of excess net fluid volume on PD target attainment need to be done to determine if initial AG doses need to be supplemented to account for this increased fluid.