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Estimated Glomerular Filtration Rate in Determining Aminoglycoside Dosing

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Chronic kidney disease (CKD) is often associated with altered pharmacokinetics of many drugs. In hospitalised patients, non-compliance with dosing guidelines for CKD patients is common, ranging from 19% to 67% [1]. Thus, patients with CKD are at risk for dosing errors and drug toxicity. Aminoglycosides such as gentamicin, tobramycin and amikacin are bactericidal antibiotics indicated for severe gram negative infections. Aminoglycoside clearance is dependent on renal function and they are also nephrotoxic. Dose adjustments are required in patients with CKD. On the other hand, under-dosing is a valid concern as rapid achievement of target concentrations is crucial for antibacterial efficacy. It is clear that an accurate assessment of renal function is required to optimise the initial dose of aminoglycosides while minimising toxicity.

The gold standard of assessing glomerular filtration rate (GFR) by radionuclide methods is impractical for guiding drug dosing. The Cockroft-Gault (CG) formula estimates creatinine clearance as a surrogate for GFR. Most guidelines and product information recommend the CG formula for estimating aminoglycoside dosing. The CG formula requires the patient weight, which may be adjusted for ideal body weight, lean body weight or body surface area to account for obese patients [2]. However, these modifications have been inconsistently applied. Recently, improved equations for estimated GFR (eGFR) have surfaced, with the addition of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas [3,4]. The MDRD formula is further modified as the isotope dilution mass spectroscopy (IDMS) traceable 4-variable equation following standardisation of creatinine assays [5]. These eGFR formulas were developed from population studies and are primarily used to detect and stage CKD. However, they represent an alternative to the CG formula for guiding drug dosing. Their main benefit is that eGFRs are readily available from automatic reporting with serum creatinines. However, their role in drug dosing is not clear.

Some studies suggest that the CG, MDRD and CKD-EPI formulas are not interchangeable and may result in different renal function estimates and antimicrobial dosing. In a study of 180 patients (mean age 85 years), Gill et al. reported that the CG and 4-variable MDRD equations produced discordant eGFRs in over 60% of patients, with only one third of patients sharing the same CKD stage [6]. Use of MDRD over CG would have resulted in a 20% discordant dose recommendation for amantadine. The study by Golik et al. (mean age 64 years) also noted that the CG and 4-variable MDRD equations produced a discordance rate of 22-36% for dosing four non-aminoglycoside antibiotics [7]. Their study cohort was non-ICU patients with stable CKD (GFR <90 ml/min/1.73 m^2). Hermsen et al. studied 372 patients (mean age 72 years) with acute (rise in serum creatinine >0.5 mg/dl for 2 days) or chronic kidney disease (GFR <60 ml/min/1.73 m^2). There was discordance in dose recommendations of 35.7% for commonly used non-aminoglycoside antimicrobial drugs [8]. In all three studies, the MDRD formula yielded higher eGFRs than CG and would have resulted in higher dosage recommendations for the drugs studied. Wargo and English studied 409 patients (mean age 73 years) and compared the CG and CKD-EPI formula [9]. Although the CKD-EPI formula yielded eGFRs 5 ml/min higher than the CG formula, they demonstrated a 15-25% discordance of non-aminoglycoside antimicrobial dosing [9]. As none of these studies evaluated actual drug concentrations, they merely suggest that the use of eGFR formulas instead of CG may yield a 20-36% discordance rate in hypothetical dosing recommendations for renally eliminated antimicrobials.

Only a few pharmacokinetic studies utilising patient-specific drug concentrations have looked at the eGFR formulas and aminoglycoside dosing. Bookstaver et al. studied 71 patients (mean age 52 years) comparing a 6-variable MDRD and body surface area-adjusted CG formulas for predicting aminoglycoside elimination rate and clearance [10]. Population based pharmacokinetic equations were used for predictions and the MDRD formula outperformed CG in this setting. MDRD was more accurate, with 29% more estimates falling within a 30% window of patient-specific aminoglycoside clearances. However, the study cohort was mainly intensive care patients and serum creatinine values were not IDMS-calibrated. Ryzner studied 55 patients (mean age 50 years) with stable renal function, comparing aminoglycoside clearance (as a surrogate for creatinine clearance) with the GFR derived from the CG (using ideal body weight) and 4-variable MDRD formula [11]. In this study, CG and MDRD yielded similar eGFRs but the CG formula yielded a higher concordance correlation coefficient with patient-specific aminoglycoside clearance, particularly with the >65 years subgroup. Pai et al. studied 2073 cases (mean age 62 years), comparing the CG, 4-variable MDRD and CKD-EPI formulas as surrogate estimates of measured aminoglycoside clearance [12]. Different weight and body surface area formula modifiers were assessed and a linear regression pharmacokinetic model was used to estimate aminoglycoside clearance. This study found that eGFR was better than CG in estimating aminoglycoside clearance, with CKD-EPI outperforming MDRD for precision in patients with eGFR >60 ml/min/1.73 m^2. The MDRD and CKD-EPI formula were comparable in patients with eGFR <60 ml/min/1.73 m^2. Charhon et al. studied 92 patients (mean age 83 years), comparing CG and 4-variable MDRD in a two compartment pharmacokinetic model [13]. Model selection was performed on an initial learning set of 64 patients utilising different weight or body surface area formula modifiers and validated in the remaining 28 patients. In this study of very elderly patients, MDRD

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