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Urinary Creatinine Clearance and Pharmacokinetics Studies: If We Can Measure It, Why Do We Estimate It?

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In a recent issue of *Antimicrobial Agents and Chemotherapy*, Aréchiga-Alvarado et al. (1) evaluated the influence of renal function on amikacin pharmacokinetics (PK) in a group of critically ill patients and concluded that there is wide variability in PK parameters, leading to inadequate dosing regimens, especially in patients with augmented renal clearance (ARC).

During critical illness, normal physiology is greatly modified, such that the PK of antibiotics, particularly those that are predominantly cleared by the kidneys, is highly variable. Urinary creatinine clearance (CR_{CL}) is frequently used at the bedside as a surrogate of the glomerular filtration rate (GFR), so as to individualize drug therapy. Popular mathematical estimates of GFR, such as the Cockcroft-Gault (CG) formula, and modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI) equations were developed primarily for detecting chronic kidney disease in non-intensive care unit (ICU) patients with stable serum creatinine concentrations (2). In addition, they have not been validated for critically ill patients.

ARC is usually defined as a CR_{CL} of $\geq$130 ml/min/1.73 m^2, is present in 20 to 65% of critically ill patients, and has been independently associated with the male sex, young age, and trauma in ICU admission diagnoses (3, 4). Of note, ARC is associated with underexposure to antibiotics and treatment failure (5–7). These findings highlight the importance of adequately measuring CR_{CL} so as to allow the correct identification of ARC and a subsequent increase of antibiotic dosing. This in turn increases the probability of successfully attaining the appropriate pharmacodynamic target. Recent recognition of the importance of ARC is the approval of cefiderocol by the Food and Drug Administration (FDA) with dosage recommendations for patients with ARC, defined as a CG-CR_{CL} of $\geq$120 ml/min (8).

Mathematical estimates have been shown to significantly underestimate measured CR_{CL} in critically ill patients with ARC (9–12). Given the poor correlation, the low accuracy, and the limited precision of these estimates in the critically ill, particularly in patients with ARC (9, 13–15), PK studies in this population should not be based on them. Studies concerning how antibiotic dosing should be adjusted with ARC are strongly encouraged. However, despite the robust evidence demonstrating that mathematical estimates are flawed, their use is still very frequent (16–18). Curiously, this methodology is frequently recognized as a limitation in such papers. Another concern regarding mathematical estimates is the fact that normalized CR_{CL} to body surface area (BSA), such as MDRD and CKD-EPI equations, although useful for comparisons of renal functions between patients or populations, should not be used for PK analysis.

Aréchiga-Alvarado et al. (1) performed their PK analysis based on CG values instead of measuring CR_{CL}. Considering that 50% of the study population included patients with ARC, in our opinion this constitutes a major limitation. In addition, recognizing that

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underestimation of CR_{CL} increases with higher values (10), the prevalence of ARC was probably even higher in the study cohort. This may have significant implications in the PK analysis, as well as in the dosing recommendations based on PK/pharmacodynamic simulations.

Utilizing estimates of renal function to predict the effects of ARC on antibiotic exposure may lead to major errors, especially in the case of critically ill patients. While it must be acknowledged that CR_{CL} is neither a perfect nor a gold standard method for evaluating renal function in acutely critically ill patients, we argue that it offers an inexpensive, reproducible, and more biologically accurate surrogate than mathematical estimates.

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