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Aminoglycoside dosing in patients by kidney function and area under the curve: the Sawchuk-Zaske dosing method revisited in the era of obesity ☆

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ABSTRACT

Initial dose selection of antimicrobials typically involves the clinical integration of covariates of drug disposition such as age, sex, weight, and kidney function. However, dynamic clinical states and unaccountable confounders necessitate our measurement of systemic concentrations in an individual patient to better inform dose modification. Over the past 50 years, several research groups have formulated weight- and kidney function–based dosing algorithms to measure, assess, and optimize the dosing of aminoglycosides. The lessons learned from older aminoglycosides may be useful and have applications to newer antimicrobials that are dosed on weight and kidney function. This is especially true among obese patients, for whom optimal dosing algorithms have not been well defined. The purpose of this review is to provide healthcare providers a historical perspective of aminoglycoside therapeutic drug monitoring followed by an updated approach to improve dosing of these agents in obese adult patients.

Over the past 4 decades, the prevalence of obesity (defined as a body mass index [BMI] ≥30 kg/m^2) among adult patients in the United States has increased from 14.5% to 35.7% (Flegal et al., 1998, 2012). This major shift in body weight distribution of the population calls into question several routine practices associated with initial drug dose selection of certain antimicrobials based on weight. Dosing of aminoglycoside antimicrobials is based on weight and kidney function, with subsequent dosage modifications guided by serum drug concentrations (therapeutic drug monitoring [TDM]) (Begg et al., 2001). The underlying basis supporting continued TDM for this antimicrobial class is the high interpatient variability in pharmacokinetic (PK) parameters, access to clinical drug assays, and relationships of aminoglycoside concentrations to efficacy and toxicity. Although clinical variables such as estimates of kidney function can help to reduce interpatient variability, most estimates are unlikely to explain more than 50% of this variability (Pai et al., 2011). As a result, the measurement or estimation of kidney function improves initial dose estimation but requires TDM to provide a reliable estimate of individual drug disposition.

Dosing recommendations of newer antimicrobial agents such as daptomycin and telavancin are also based on weight and kidney function but TDM is not readily available (Cubicin, 2010; Vibativ, 2012). The lack of easy access to drug assays for these agents may be problematic because kidney function is not reliably estimated in all patient populations, especially among individuals at the extremes of the weight distribution (Park et al., 2012).

Numerous equations exist to estimate kidney function using the surrogate creatinine clearance (*CLcr*) in adults across the weight distribution (Pai, 2012). Creatinine is an endogenous biomarker that is a by-product of creatine metabolism by skeletal muscle. The rate of creatinine elimination is dependent on glomerular filtration and to some degree by renal tubular secretion. Because serum concentrations of creatinine depend on skeletal weight, its production does not increase in proportion to total body weight (TBW), which also represents fat weight. As a result, use of TBW to estimate kidney function that relies on serum creatinine (SCr) tends to overestimate kidney function in obese adults. This inaccurate estimation of kidney function can lead to erroneously higher antimicrobial doses and subsequent toxicity in obese adults.

Several approaches have been developed to correct this kidney function overestimation problem in obese adults (Pai, 2010). However, these corrections are rarely validated in a prospective fashion and require reappraisal by regulatory bodies in order to inform the dose label. As a result, the actual dosing of antimicrobials that are dosed on weight and kidney function is expected to be highly variable in clinical practice. This TDM challenge has recently been tackled through the innovative approach of co-modeling drug concentration-time data. Although differences exist between tubular reabsorption of aminoglycosides, the clearance (CL) of gentamicin,

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tobramycin, and amikacin can serve as close approximation of the glomerular filtration rate (GFR) (Contrepois et al., 1985). So the measurement of aminoglycoside concentrations in an individual may be a more reliable estimate of kidney function than estimation based on creatinine. Research groups have utilized this approach to better predict β-lactam doses using amikacin TDM (Delattre et al., 2012).

The current review provides a detailed summary of the strengths and limitations of kidney function estimation in obese adults. A synopsis of the literature regarding the relationships of body size, kidney function, and aminoglycoside disposition is provided. A historical perspective on the development of the current aminoglycoside therapeutic range is included. Our interpretations of available aminoglycoside dosing recommendations and a future perspective on dosing these agents in obese patients are detailed.

1. Estimation of kidney function in obese adults

The CL of drugs from the systemic circulation by the kidneys is driven by glomerular filtration, tubular secretion, and tubular reabsorption. Measurement of the GFR is best achieved through the exogenous administration of substances such as inulin that is not prone to renal drug influx and efflux transporters (Gaspari et al., 1997). Unfortunately, the technical complexity for measurement of inulin CL as a marker of GFR leads to the clinical estimation of kidney function by the surrogate parameter *CLcr* (Park et al., 2012). Several transporters of the solute like carrier (*SLC*) and adenosine triphosphate binding cassette (*ABC*) families regulate in part the secretion and reabsorption CL mechanisms of compounds by the kidney. Creatinine is specifically secreted by human organic cation transporter 1 of the SLC family (Urakami et al., 2004). Because secretion plays a role in the elimination of creatinine, *CLcr* intrinsically overestimates GFR by approximately 5–15% (Park et al., 2012). *CLcr* can be measured through the assay of concentrations in serum and urine via a 24-hour collection but is cumbersome and also prone to urine collection errors. As a result, estimation of *CLcr* using SCr is the most common approach used to provide point estimates of kidney function.

Dosing of several antimicrobials including the aminoglycosides, vancomycin, daptomycin, and telavancin is based on *CLcr* using the Cockcroft-Gault equation (Cubicin, 2010; Pai et al., 2011; Vancomycin hydrochloride, 2008; Vibativ, 2012). The specific limitations of this equation including the implications of conversion to isotopic dilution mass-spectrometry standardized assays have been detailed by several groups (Atkinson and Huang, 2009; Brater, 2009; Spruill et al., 2009; Stevens and Levey, 2009). One argument would be to continue to dose these antimicrobial agents based on the regulatory approved product labels, which often state the use of Cockcroft-Gault equation (Cockcroft and Gault, 1976). However, the availability of alternate equations such as the Chronic Kidney Disease Epidemiology Group (CKD-EPI) that enhance the precision of GFR estimation could help to improve upon this historic approach (Levey et al., 2009). The CKD-EPI equation is particularly noteworthy in that it reduces the overestimation bias of kidney function equations when the SCr value is <0.9 mg/dL (males) or <0.7 mg/dL (females) and does not include body weight as a covariate. However, the specific influence of race on this equation remains a topic of contention (Earley et al., 2012; Stevens et al., 2011). Although GFR estimation equations are useful for staging kidney disease, their predictive performance for drug dose adjustment has not been systematically validated for broad adoption.

In contrast to GFR estimation for staging, the clinical decision pathway is inconsistent regarding body size descriptors when using the Cockcroft-Gault equation in product labels for drug dosing (Pai, 2012). A review of United States Food and Drug Administration approved product labels reveal that: 1) gentamicin and tobramycin dosing recommendations are based on SCr or *CLcr* scaled to body surface area (Pai et al., 2011); 2) amikacin dosing is based on *CLcr* but the approach is poorly specified (Pai, 2012); 3) daptomycin dosing is based on the Cockcroft-Gault equation and use of TBW (Cubicin, 2010); and 4) telavancin dosing is based on the Cockcroft-Gault equation and use of ideal body weight (IBW) (Vibativ, 2012).

The numerous caveats that currently exist with the measurement, estimation, and interpretation of kidney function values are undoubtedly complex to manage in the clinic (Park et al., 2012). However, it is critical for healthcare providers to recognize the positive and negative bias that can be introduced with the use of certain equations for obese individuals. To date, the specific changes in the influx and efflux transport mechanisms of the kidneys in obese compared to normal weight individuals have not been well characterized (Pai, 2010). However, GFR is known to increase with body size and has been shown to be higher in obese individuals compared to age, sex, and disease-state matched normal weight adults (Chagnac et al., 2008). This increase in GFR does not consistently occur in direct proportion to TBW.

One key reason for this inconsistency is a phenomenon known as glomerular hyperfiltration. Glomerular hyperfiltration has been defined as a GFR value >140 mL/min/1.73m^2 and has been observed in 10–30% of obese patients, especially among those with diabetes and hypertension (Chagnac et al., 2008; Frische, 2011). Glomerular hyperfiltration can contribute to glomerular injury over time and lead to chronic kidney disease (Frische, 2011). Unfortunately, detection of this phenomenon requires the measurement of the filtration fraction that is a ratio of GFR and the effective renal plasma flow (ERPF) (Chagnac et al., 2008). This measurement error has likely confounded our ability to assign an appropriate body size descriptor to estimate kidney function in morbidly obese adults. The Cockcroft-Gault equation is the most common estimate used to aid drug dose adjustment, and it relies on TBW. This is in contrast to GFR estimation equations CKD-EPI and Modification of Diet in Renal Disease (MDRD) that do not include TBW as a system parameter for estimation of kidney function (Pai, 2010). Instead, measurement and estimation of GFR over the past century have normalized kidney function to body surface area (BSA) (Mosteller, 1987).

Most equations used to estimate BSA are based on a power function of TBW$^{\beta}$ and height$^{\alpha}$ and follow a Euclidean geometric paradigm, which leads to the basic assumption that BSA $\propto$ TBW$^{0.67}$ (Pai, 2012). Although some have argued this body size scalar to be equally spurious, the conceptual framework remains that kidney function and drug CL increase as a nonlinear function of TBW. The mathematical assumptions that have led to these scalars have recently been described in detail. Thus, TBW is more likely to be incorrect if used in the Cockcroft-Gault equation to estimate kidney function in morbidly obese adults (Pai, 2012).

Consequently, alternate approaches to improve the estimation of kidney function in obese adults have historically attempted to define body weights that are more representative of lean body weight (LBW). This desire to quantify LBW stems from the assumption that adipose tissue does not play a significant role in physiological pathways of xenobiotic CL. Subtraction of this 'fat-weight' from TBW has been the simplest way to estimate LBW or fat free weight. Several equations have been developed to estimate LBW and have been formulated as linear and non-linear functions of weight and height with regard to sex (Pai, 2012). Estimation of LBW has also included the use of actuarial (New York Metropolitan Life Insurance) height-weight tables of "desirable" weights based on the height (with shoes on), sex, and frame size of adults (Pai and Paloucek, 2000). These weights were considered desirable because they were associated with the lowest probability of mortality. The term "desirable" was semantically transformed to imply 'ideal' body weight. This IBW was further erroneously translated to imply LBW but is physiologically incorrect because LBW increases with both height and TBW, while IBW is assumed to increase only with height. This limitation of IBW as an estimate of LBW has been corrected by assuming that 30–40% of the difference between the estimate of IBW and TBW