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Use of Creatinine Clearance Estimates in Pharmacokinetics

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Estimates of creatinine clearance (Clcr) are frequently applied to assess the influence of renal disease on drug pharmacokinetics and also to adjust medication doses in patients with varying degrees of renal function. The literature contains an enormous number of proposed Clcr prediction methods as well as their evaluation. To assess these approaches such as the Cockcroft-Gault (CG) [1] and the MDRD methods [2], the estimates by these methods are compared to diagnostic tests such as inulin clearance, Cr-EDTA or Tc-DTPA measurements of Clcr. Performing renal diagnostic tests are not realistically possible in routine clinical practice. It is recognized that serum creatinine based methods are flawed in many ways by such factors as contributions of creatinine secretion, variation among serum creatinine assays, effects of muscle mass, dietary issues, metabolic disease, its retrospective nature, and drug interactions.

Despite the many years of research and applications of these serum creatinine-based methods to predict Clcr, there still appears to be some confusion regarding whether the creatinine clearance estimates should be adjusted or normalized for weight or surface area. Product dosing information and FDA guidances frequently classify the degree of renal function in terms of ml/min instead of ml/min/70 kg lbw or /1.73 m^2. The recent FDA guidance related to pharmacokinetics studies in renal dysfunction subjects also suggests a MDRD method based on /1.73 m^2 as well as the non-adjusted CG (mL/min) approach [3].

In understanding the influence of renal dysfunction on pharmacokinetics and for dose adjustment, the fraction of normal renal function is more important than the particular Clcr as mL/min. The fraction would be the weight or surface area normalized (70 kg or 1.73 m^2) creatinine clearance divided by 120 mL/min/70kg or /1.73 m^2, respectively. LBW instead of total body weight may be better. For instance, a patient with a Clcr of 70 mL/min and a surface area of 1.3 m^2 (1.73-25%) has a function fraction of 0.776 where as another patient of 2.16 m^2 (1.73+25%) with the same 70 ml/min would have function of 0.458. These patients would have ml/min/1.73 m^2 estimates of 93.2 and 55.0 corresponding to normal (>90) and moderately decreased (30-59) renal classification groups, respectively.

Whether obtained theoretically or obtained from clinical studies, predictive equations of total body clearance (Clt) and the eliminations constant (Ke) based upon Clcr are useful in designing dosage regimen in renal dysfunction patients. For example, Ke can be predicted as (a)(Clcr)+km and Clt as (A)(Clcr)+Clm. Where km and Clm are constants for metabolism unchanged by renal function and "a" and "A" are proportionality constants for predicting ke, the renal elimination rate constant, and Clr, the drug renal clearance, based upon Clcr. In example, using the equation that Ke (hr-1) = 0.0024 Clcr + 0.01 and considering the above two patients with Clcr of 70 mL/min, the first patient (1.3 m^2) 'would have a $t_{1/2}$ of 3.0 hr and the second (2.2 m^2) would have a predicted $t_{1/2}$ of 4.9 hr. With this equation and using 70 mL/min/1.73m^2, the $t_{1/2}$ is 3.0 hr. The value of Ke and $t_{1/2}$ are functions of the degree of renal function but not of the patient's size or weight.

Through the years, researchers and practioners become more aware of the use or misuse of Clcr and prediction equations. In most cases, weight or surface area normalized Clcr values are the most appropriate for patient classifications, drug dosing, and traditional and population modeling.

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