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A Physiological Approach to Renal Clearance - from Premature Neonates to Adults

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Poster: Clinical Applications

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Objectives: A physiological basis to hepatic drug clearance has been widely applied based on the identification of hepatic blood flow as a key determinant of hepatic clearance. We propose individual predictions of glomerular filtration rate (GFR) as a physiological basis for identifying the components of renal clearance.

Methods: Gentamicin, amikacin and vancomycin are thought to be predominantly excreted by the kidneys. A mixed effects joint model of the pharmacokinetics of these drugs, with a wide dispersion of weight, age, and serum creatinine, was developed (NONMEM 7.5.0) by pooling data from 18 sources from around the world resulting in 27,341 drug concentrations in 9,951 patients. Normal GFR for each individual is based on the assumption of absence of kidney disease and calculated using demographic factors. GFR clearance was assumed to approach an asymptotic value determined by normal GFR. Non-GFR clearance was not constrained by normal GFR. Body size and composition, maturation and renal function (defined as the ratio of estimated GFR to normal GFR) were used to describe individual differences in drug clearance. Details of the calculation of fat free mass, creatinine production rate, creatinine clearance, estimated GFR, normal GFR and renal function (RF) are described in (1). Normal fat mass (2) was estimated for both clearance components and for distribution parameters in order to account for differences in body composition.

Results: This study confirms that GFR is a predictor of drug elimination clearance with two distinct components, GFR clearance associated with individual normal GFR and non-GFR clearance not associated with GFR. Individual differences in GFR clearance were related to renal function with an asymmetrical sigmoid function. The inclusion of RF in a distinctly different function (directly proportional rather than sigmoidal) as a predictor of non-GFR clearance was an key factor distinguishing GFR clearance from non-GFR clearance. The link with RF makes it likely that non-GFR clearance is describing a different mechanism of renal excretion that is not explained simply by GFR.

All three drugs had GFR clearance estimated as a drug specific percentage of normal GFR (gentamicin 39%, amikacin 88%, vancomycin 55%). This is comparable to the finding that a linear function of creatinine clearance explains only 76% of aminoglycoside clearance (3).

The total clearance (sum of GFR and non-GFR clearance), standardized to a 70 kg, 176 cm, adult male and renal function of 1, was 5.67 L/h (95% CI 5.44-5.90) (gentamicin), 7.51 L/h (95 %CI 7.15-7.83) (amikacin) and 4.82 L/h (95 %CI 4.79-5.04) (vancomycin).

A drug specific maturation of size and composition scaled volume of distribution was observed with an initial increase at birth relative to an adult for both central volume (58% gentamicin, 35% amikacin, 4.7% vancomycin) and peripheral volume (1.5% gentamicin, 25% amikacin, 2.5% vancomycin). The maturation of volume falls exponentially to just 5% above adult values by 3.01 years (central volume) and 3.16 years (peripheral volume).

Conclusion: GFR provides a physiological basis for renal drug elimination. It has been used to distinguish two elimination components using two compartment pharmacokinetic distribution model for gentamicin, amikacin and vancomycin. This physiological approach has been applied to describe total clearance from premature neonates to elderly adults with a wide range of sizes and renal function. Given a target exposure then the dose needed to achieve the target can be predicted based on this model e.g. using a steady state vancomycin target area under the curve of 500 mg/L*h over 24 h then the dose may be calculated by multiplying the individual total clearance (L/h) by 500 (mg/L*h) to predict the total daily dose (mg).