Real World Data – Realistic Population -- Evidence for Unrecognized Pharmacokinetics of Renally Eliminated Drugs

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A physiological approach to renal clearance: From premature neonates to adults

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Abstract

Aims: We propose using glomerular filtration rate (GFR) as the physiological basis for distinguishing 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 was developed, with a wide dispersion of weight, age and serum creatinine. A dataset created from 18 sources resulted in 27,338 drug concentrations from 9,901 patients. Body size and composition, maturation and renal function were used to describe differences in drug clearance and volume of distribution.

Results: This study demonstrates that GFR is a predictor of two distinct components of renal elimination clearance: (1) GFR clearance associated with normal GFR and (2) non-GFR clearance not associated with normal GFR. All three drugs had GFR clearance estimated as a drug-specific percentage of normal GFR (gentamicin 39%, amikacin 90% and vancomycin 57%). The total clearance (sum of GFR and non-GFR clearance), standardized to 70 kg total body mass, 176 cm, male, renal function 1, was 5.58 L/h (95% confidence interval [CI] 5.50-5.69) (gentamicin), 7.77 L/h (95% CI 7.26-8.19) (amikacin) and 4.70 L/h (95% CI 4.61-4.80) (vancomycin).

Conclusions: GFR provides a physiological basis for renal drug elimination. It has been used to distinguish two elimination components. This physiological approach has been applied to describe clearance and volume of distribution from premature neonates to elderly adults with a wide dispersion of size, body composition and renal function. Dose individualization has been implemented using target concentration intervention.