A general empirical model for renal drug handling in population pharmacokinetic analyses.

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Objective
Dose adjustment in renal insufficiency is generally based on the assumption that renal drug clearance is related linearly to glomerular filtration rate (GFR). It is unclear if this is reasonable for drugs that are extensively handled by tubular mechanisms. The aim of this work is to propose a general empirical model for renal drug handling.

Methods
Two general empirical models for renal drug handling were tested. The first assumes a linear relationship between GFR and renal drug clearance, given by:

\[ CL_R = \sum_{i=1}^{3} f_u \times \beta_i \times GFR = \theta \times GFR \]  

(eq 1)

where \( f_u \) is the fraction unbound, \( \beta_i (i = \{2, 3\}) \) describes the proportionality of tubular processes (set to 1 for GFR), and, \( \theta \) is the sum of GFR and tubular processes.

The second model relaxes the assumptions of linearity, given by:

\[ CL_R = \sum_{i=1}^{3} f_u \times \beta_i \times GFR^{\gamma_i} = \theta \times GFR^{\gamma} \]  

(eq 2)

where \( \beta_1 = \delta_1 = 1 \), and, \( \delta \) describes the degree of divergence from linearity for each tubular process. The exponents can be summed to get the conglomerate parameter, \( \gamma \).

Experimental data from a study by Maiza et al [1] was digitally extracted from published plots. The authors induced damage to the nephron experimentally in rats and measured the clearance of probes for renal excretory processes, including inulin, paraminohippurate, n-1-methylnicotinamide, and cimetidine. The data were pooled and model fit was assessed using NONMEM v.7.2.

Results
The best fit model is given by \( CL_{\text{probe}} = 1.58 \times GFR^{0.28} \). Introducing random effects did not improve the model fit or provide evidence that the different probes followed different relationships. The model provides a fit to the data that could not be achieved under the assumption of linearity between GFR and renal drug clearance.

Conclusions
We propose a parsimonious extension to the commonly used linear model for renal drug handling. This model has properties that allow for linearity between drug clearance and GFR and should be examined on a case by case basis.

References