

EXTRAPOLATING HUMAN DRUG CLEARANCE FROM A SINGLE ANIMAL SPECIES USING THE ALLOMETRIC PRINCIPLE WITH A FIXED SCALING EXPONENT

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We investigated the feasibility of extrapolating human drug clearance (CL) from a single animal species using simple allometry with a fixed body-weight exponent. CL values from rat, monkey, dog and human for 109 compounds were obtained from the literature. A normalization procedure based on the concept of a characteristic CL value was first introduced to homogenize and pool the CL data for a regression analysis. The allometric exponent from the regression analysis was then used as the exponent for CL extrapolation. The prediction performance of the proposed method was compared with methods that incorporate liver blood flow (LBF) or maximum life-span potential (MLP). An allometric exponent of 0.67 (95% CI, 0.64 to 0.71) adequately described the pooled CL data. A fixed value of 0.67 as the body-weight scaling exponent and monkey CL provided the best estimate of human CL, followed by rat and dog. CL prediction by the LBF approach was comparable to that of the fixed-exponent method. The MLP approach systematically underestimated the human CL. It is feasible to predict human drug CL from CL measured in a single animal species using simple allometry with a fixed body-weight exponent of 0.67. While monkey provided the best estimate of human CL, rat, but not dog, provided an acceptable prediction when monkey data are unavailable.