How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation

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Propositions to the thesis « How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation »

1. Using PBPK-based simulations, the impact of age-related physiological changes on the plasma clearance of drugs with different properties can be investigated in order to define scenarios based on age and drug variables that systematically lead to accurate plasma clearance scaling. *This thesis*

2. There is no evidence for a universal allometric exponent to scale size-related changes in drug plasma clearance from adults to children. *This thesis*

3. Between-drug extrapolation of pediatric covariate functions for plasma clearance is applicable to drugs with low and intermediate extraction ratios eliminated by one isoenzyme and binding to human serum albumin in children older than 1 month. *This thesis*

4. Being able to *a priori* define trial requirements that yield numerical identifiability, is essential for resource-efficient and ethical pediatric clinical trial design. *This thesis*

5. In the very young, only scaling methods that take drug properties and isoenzyme maturation into account have a rational basis for systematically accurate prediction of pediatric plasma clearance. *This thesis*

6. Since the aim of estimating the allometric exponent during clinical pharmacokinetic data analysis is not to accurately estimate the exponent, but to estimate an exponent that allows for accurate clearance predictions, bias in the allometric exponent should be assessed based on its impact on the accuracy of clearance values. (*Adapted from J. Sinha et al., Clin. Pharmacokinet. 2018 Apr. 27, epub ahead of print*)

7. With the increase in computing power and progress in systems pharmacology modelling, sharing the ever increasing amount of medical data is ethically the right choice for everyone in healthcare. (*Adapted from K. Fultz Hollis, AMIA Jt Summits Transl Sci Proc. 2016: 420–427*)

8. While a theory cannot be proven, its disproof forms building blocks for new theories.

9. Communication between pharmacometricians and clinicians is mandatory to bring pharmacological headway to the patient's bedside. (*Adapted from L. Restifo and G. Phelan, Dis. Model Mech. 2011: 423–426*)

10. Conventional wisdom puts a break on the advancement of sciences.

11. Ethics consists of subjectively drawing a line between what you have a right to do and what is right to do, while remaining objective. (*Adapted from Potter Stewart*)

12. The world is not binary, but our vision of it might be.

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