An Analysis of the Need for an Additional Toxicokinetic Uncertainty Factor for Neonates

Namali V. Corea and Andrew G. Renwick. *Clinical Pharmacology Group, University of Southampton, UK.*

The objective of this study was to evaluate the interspecies and age-related differences in the internal dose (toxicokinetics) of chemicals that are cleared from the body by the major routes of elimination in humans. The in vivo pharmacokinetics of compounds, which are probe substrates for different pathways of adult human xenobiotic metabolism, were evaluated experimentally in immature and adult rats, and compared with the equivalent published pharmacokinetic values for the same compounds in human neonates, infants, children and adults. The data provided a scientific assessment of the appropriateness of the default interspecies uncertainty factor when the reference dose (RfD) value is based on effects seen in young rats. Several therapeutic drugs have been identified from published studies, for which data are available in young and adult humans, that are probe substrates for the metabolic (Phase I and Phase II metabolism) and renal elimination of chemicals.

Plasma kinetic profiles were defined in groups of adult and 10-day-old rats administered a particular probe substrate. Animals received a single intraperitoneal dose of 200 mg/kg chloramphenicol (metabolized by glucuronyltransferase), 5 mg/kg caffeine, 50 mg/kg caffeine or 50 mg/kg theophylline (metabolized by CYP1A2), 5 mg/kg midazolam (metabolized by CYP3A4), or 500 mg/kg amoxycillin (eliminated by renal clearance).

Clearance values (ml/min/kg) were compared to equivalent published data in human neonates, infants, children and adults. The ratios of the clearance in rats to the clearance in age-equivalent humans for each substrate were then compared to the default inter-species toxicokinetic factor of 4. Elimination was generally more efficient in rats compared to age-equivalent humans, and the default factor was slightly exceeded for human neonates for chloramphenicol and caffeine (at both doses). However, the clearance of midazolam was much higher in rats and the default interspecies factor of 4.0 was exceeded by 5.6-fold for neonates. These data indicate that an additional uncertainty factor for neonates may be warranted for compounds eliminated mainly by CYP3A4. Overall an additional 10-fold factor for infants and children as proposed by the FQPA would be excessive in relation to toxicokinetic differences between young rats and human neonates, infants and children.

Start and end date: January 2001 - January 2004

Presentations:


This abstract was prepared by the principal investigator for the project. Please see www.USLRI.org for more information about the LRI.


Peer-reviewed publication(s): None to date.

Other publication(s): None.

Sponsors in addition to the LRI: None.

Abstract revision date: January 2006.

This abstract was prepared by the principal investigator for the project. Please see www.USLRI.org for more information about the LRI.