DEVELOPMENTAL PK/PD: WHAT HAVE WE LEARNT?

Geoff Tucker
UNDERSTANDING AND PREDICTING PK/PD IN JUVENILES
Can we scale from juvenile animals?

Can we scale from allometry?

Can we scale from in vitro?
ORAL BIOAVAILABILITY

% Adult

HUMAN CYP3A4
(Johnson et al, 2006)

♂ RAT CYP3A1
(Johnson et al, 2000)

♀ RAT CYP3A1
(Johnson et al, 2000)

DOG CYP3A12
(Taneka, 1998)

neonate  infant  child  adolescent  adult
ONTOGENY OF TRANSPORTERS (ANIMALS)

Liver
- Pgp
- Mouse (Mahmood et al, 2001)

Intestine
- Pgp
- Rat Brain (Matsouka et al, 1999)

Kidney
- Oatp
- Rat Kidney (Buist et al, 2002)

Bile salt/OATs - Rat Liver
- Gao et al, 2004

OATs - Rat Kidney
- Buist et al, 2002
<table>
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"THE 3/4 (Klieber's) LAW"

From allometric principles:

$$\text{Metabolic Rate } \propto \text{BW}^{0.75}$$

$$\text{Clearance } \propto \text{BW}^{0.75}$$

Holford - “A size standard for pharmacokinetics”
“THE 3/4 (Klieber’s) LAW”

From measurements in 5036 N.Europeans, N.Americans and Japanese:

Liver Volume = 0.722 \times BSA^{1.176} 

BSA \propto BW^{0.67} 

Liver Volume \propto BW^{0.78} 

Clearance \propto BW^{0.78} 

Johnson et al - “Changes in liver volume from birth to adulthood: a meta-analysis” 
Liver Transpl 11: 1481-93, 2005
Johnson et al: \( LV = 0.722 \times BSA^{1.176} \)

Allometric: \( LV_{\text{child}} = LV_{\text{adult}} \times \left( \frac{BW}{70\text{kg}} \right)^{0.75} \)
Liver Volume (L)

- LV = 0.722 x BSA^{1.176} \ (n = 162 \ patients)
- LV = 1.46 x (BW/70kg)^{0.75}

Fanta et al - “Developmental pharmacokinetics of ciclosporin: A population pharmacokinetic study in paediatric transplant patients
The ‘3/4 Rule’ holds for predicting the clearance of several drugs (e.g. CYP3A substrates—ciclosporine, midazolam, alfentanil etc)

But it does not account for the ontogeny of drug metabolising enzymes in neonates and infants.

Use ‘3/4 Rule’ to normalise clearance only > 2 years.
Can we scale from juvenile animals?

Can we scale from allometry?

Can we scale from *in vitro*?
AGE-RELATED CHANGES IN CYP EXPRESSION/ACTIVITY


1A2
2B6
2C8
2C9
2C19
2D6
2E1
3A
EFFECT OF DIET ON CAFFEINE ELIMINATION RATE CONSTANT (CYP1A2)

GLUCURONONIDATION

Time to maturity?

UGT1A1 (e.g. ethinylestradiol) < 6 months
UGT1A4 (e.g. imipramine) < 2 years
UGT1A9 (e.g. propofol) > 2 years
UGT2B4 > 2 years
UGT2B7 (e.g. morphine) < 6 months

Strassburg et al, 2002; Miyagi & Collier, 2007
Predicting Paediatric Clearance

Johnson et al.
Clin Pharmacokin 2006
Below ~ 2 years - prediction of clearance is drug specific due to differential development of its determinants.
• Incorporating information on organ size, tissue composition and blood flow
• Allows for prediction of full PK profile ($V$, $MRT$, $C_{\text{max}}$, $C_{\text{min}}$)
PK MODELLING

"TOP DOWN"

- Plasma Data
- POPPK
- PBPK/IVIVE
- Confirming
- Learning

"BOTTOM UP"

Demography, Physiology, Genetics, In Vitro Data
# PHARMACODYNAMICS

## Age-Related Changes in Concentration-Response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age Range</th>
<th>n</th>
<th>Observation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1 - 76y</td>
<td>134</td>
<td>Increased CR effect (INR/dose) in 1-11y group</td>
<td>Takahashi et al (2000)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Preterm - 29w</td>
<td>31</td>
<td>Decreased CR (sedation)</td>
<td>De Wildt et al (2001)</td>
</tr>
</tbody>
</table>
MIDAZOLAM (10mg/kg S/C – Rats)

Latency to right (secs)

Postnatal Age (days)


Baseline

After midazolam

“Dynamic mapping of human cortical development during childhood through early adulthood”

Gogtay et al - PNAS 101: 8174, 2004
PK-PD MODELLING

“Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis”


“A 50% increase in dose would increase odds ratio from 4 to 275 in favour of sedation score 2 (drowsy/asleep) at start of surgery”
An indirect response model of homocysteine suppression by betaine: optimising the dosage regimen of betaine in homocystinuria

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Br J Clin Pharmacol 54:140, 2002

- Homocysteinuria
  (3 in 1 million)
- Betaine
  (orphan drug)
- Limited population of patients to study
- No Pharma funding for large studies

Solution: Clinical Trial Simulation

\[
\frac{dH}{dt} = k_{in} - k_{out} S(t) H(t)
\]

\[
S(t) = 1 + \frac{E_{Max} C_{Betaine}(t)}{E C_{50} + C_{Betaine}(t)}
\]
Increase in the usual daily dosage (150 mg/kg) or in dosage frequency greater than twice daily is predicted to give negligible added clinical benefit for an additional cost of £2100 per patient year and potential decrease in compliance. Two divided daily doses may be optimal.
Concentrate on < 2 year olds
- More variable
- High risk
- Developing systems

More ‘creative’ PD evaluation