Considerations on first paediatric dose, safety and therapeutic range for different age groups

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Tensión arterial
Celulitis
Diabetes
Eliminar grasas
Gastritis y gases
Tos y anginos
Gripe
Colesterol
No tocar
Gabapentin (Neurontin)

Anti-epileptic

*absence of effect in the first studies because of insufficient dosing*
Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study

Esse N Menson, A Sarah Walker, Mike Sharland, Carole Wells, Gareth Tudor-Williams, F Andrew I Riordan, E G Hermione Lyall, Diana M Gibb, for the collaborative HIV paediatric study steering committee

**Fig 2** Recommended daily doses of nevirapine calculated from surface area or weight for each individual measurement of weight and height in CHIPS
Take home message 1

Children are different

specific diseases
pathophysiology
maturation
interindividual variability

PATTERN RECOGNITION
PREDICTABILITY
Considerations on first dose, safety, therapeutic range

Selecting a population

Selecting a dose
  best attempt

Getting the drug in the patient
  formulation

PK assessment
fetus
  ↓
newborn
  ↓
infant
  ↓
toddler
  ↓
child
  ↓
adolescent
  ↓
adult

weight x 2  5 m
x 3  1 y
caloric needs x 3-4  1 y

Adolescence: transition to adulthood, puberty
Body composition
Age-dependent

Formula dependent

Ref: Kearns et al, NEJM 2003
Vd hydrophylic drug: paracetamol
**Vd lipophylic drug: propofol**

Figure 2
Apparent volume of distribution at steady state ($V_{ss}$, l·70 kg$^{-1}$) estimates in 31 patients with age range from 27 weeks postmenstrual age (PMA) to 7 years (equivalent to 405 weeks PMA). The continuous line estimates a variable slope sigmoid function between distribution volume ($V_{ss}$) and age (PMA).

$x$-axis: postmenstrual age (weeks); $y$-axis: (l·70 kg$^{-1}$).
Body composition
Age-dependent

Hepatic

Renal

Formula dependent

Ref: Kearns et al, NEJM 2003
Drug-metabolisme: co-variates

Polymorphisms
(e.g. CYP2D6)

Age
Weight

Iso-enzyme specific
phenotypic activity

co-morbidity
(e.g. type of surgery)

Environmental
(e.g. maternal smoking
co-medication)
Fig. 2 The metabolic rate or metabolic power expressed in Watts (or kcal or MJ) vs. mass. The figures are adapted from Gillooly et al. (2001, 2002) and West and colleagues (West et al., 1997, 1999, 2002; West and Brown, 2005). Metabolic rate can be shown to scale across approximately 18 orders of magnitude of mass or weight. Energy utilization by unicellular components also allometrically scales with a high degree of precision.
**Table 1** Paediatric maintenance doses of drugs expressed as a percentage of adult dose using an allometric 3/4 power model. The neonatal estimate based on size has been reduced further by 50% to account for age-related maturational changes of clearance. (Modified from Holford and Anderson (1997) Paediatric dosages. In: New ethicals catalogue. Adis International, Auckland, New Zealand, C9)

<table>
<thead>
<tr>
<th>Approximate age</th>
<th>Weight (kg)</th>
<th>Percentage of adult dose</th>
<th>Fraction of adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>3.2</td>
<td>5</td>
<td>1/20</td>
</tr>
<tr>
<td>2 months</td>
<td>4.5</td>
<td>13</td>
<td>1/8</td>
</tr>
<tr>
<td>4 months</td>
<td>6.5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>10</td>
<td>23</td>
<td>1/4</td>
</tr>
<tr>
<td>18 months</td>
<td>11</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>18</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>7 years</td>
<td>23</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>30</td>
<td>53</td>
<td>1/2</td>
</tr>
<tr>
<td>11 years</td>
<td>36</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td>40</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>14 years</td>
<td>45</td>
<td>72</td>
<td>3/4</td>
</tr>
<tr>
<td>16 years</td>
<td>54</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>70</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>
Allometric relationships between the pharmacokinetics of propofol in rats, children and adults
Observations in 25 neonates, population PK

(A)

(B)

(C)

(D)

Br J Anaesth 2007
drug metabolism: polymorphism

**Genotype**

**Drug Metabolism (Degradation)**

- WT/WT: \[\text{AUC}=100\]
- WT/V: \[\text{AUC}=200\]
- V/V: \[\text{AUC}=400\]

**Drug Receptor (Efficacy)**

- % Responding vs. AUC
- Efficacy vs. Toxidity

**Polygenic Drug Response**

<table>
<thead>
<tr>
<th>Metabolism genotype</th>
<th>Receptor genotype</th>
<th>Efficacy</th>
<th>Toxidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>6.9%</td>
<td>Low (5%)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>32%</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>9%</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>79%</td>
<td>Moderate (1.5%)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>40%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>10%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>80%</td>
<td>High (80%)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>40%</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>10%</td>
<td>High</td>
</tr>
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</table>
Developmental changes in gene expression and/or functional activity of a hypothetical gene for the first 25 years of life for 20 individuals.
M1 Formation Clearance (L/h/70kg)

PMA (weeks)

- CYP 1
- CYP 2
- CYP 3
- CYP 0

(pop CYP2)

(pop CYP1)
Case report

Apnea in a child after oral codeine: a genetic variant – an ultra-rapid metabolizer

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Summary
We present a case of a 29 months old previously healthy child who experienced apnea resulting in brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anesthetic for tonsillectomy. A genetic polymorphism leading to ultra-rapid metabolism of codeine into morphine resulted in nargosis and apnea. This paper discusses the use of codeine for pain relief, obstructive sleep apnea, the alteration of the CYP2D6 gene and the resulting effect on drug metabolism.

Keywords: codeine; complications; apnea; genetic polymorphism; pediatrics; obstructive sleep apnea
Clearance of Morphine in Postoperative Infants During Intravenous Infusion: The Influence of Age and Surgery

Anne Lynn, MD1, Mary Kay Nespeca, RN1, Susan L. Bratton, MD1, Susan G. Strauss, MD1, and Danny D. Shen, PhD†

Departments of *Anesthesiology and †Pharmaceutics, University of Washington School of Medicine; and †Department of Anesthesia and Critical Care, Children’s Hospital and Medical Center, Seattle, Washington

We analyzed morphine clearance values in infants receiving the drug by continuous IV infusion for analgesia after surgery, because we found lower steady-state morphine concentrations than we expected from our previous studies. Infants received morphine after a loading dose of 0.05 mg/kg and continuous infusion calculated to reach a steady-state concentration of 20 ng/mL. Blood was sampled twice on Postoperative Day 1 at times separated by at least 2 h, and morphine and morphine-6-glucuronide (M-6-G) concentrations were determined by high-performance liquid chromatography. Clearance of morphine was calculated as infusion rate divided by the steady-state morphine concentration. Morphine given to 26 infants by continuous IV infusion after major noncardiac surgery has rapidly increasing clearance values, from a median value of 9.2 mL/min·kg−1 in infants 1–7 days old, 25.3 in infants 31–90 days old, and 31.0 in infants 91–180 days old to 48.9 in infants 180–360 days old. Adult clearance values are reached by 1 mo of age, more quickly than in infants of the same age previously studied who received morphine after cardiac surgeries. M-6-G was measured in all infants. The ratio of M-6-G to morphine concentrations was 1.9–2.1 in these infants, which is lower than ratios reported in older infants or adults by others, but higher than those reported in newborns. Infants with normal cardiovascular systems undergoing surgery clear morphine more efficiently than infants of the same age undergoing cardiac surgery. Implications: Morphine removal from the body is slow in newborns but increases to reach adult values in the first months of life. Calculating the clearance of morphine from blood samples drawn during continuous IV infusions after surgery shows that this maturation occurs more quickly in infants undergoing noncardiac surgery (by 1–3 mo of age) than in those receiving morphine after cardiac surgery (by 6–12 mo of age).  
Elevated Morphine Concentrations in Neonates Treated With Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy

Anikó Róka, MD, Kis Tamas Melinda, MD, Barna Vásárhelyi, PhD, Tamás Machay, PhD, Denis Azzopardi, MD, Miklós Szabó, PhD

*First Department of Paediatrics, Semmelweis University, Budapest, Hungary; †Research Group of Paediatrics and Nephrology, Hungarian Academy of Sciences, Budapest, Hungary; ‡Division of Clinical Sciences, Hammersmith Campus, Imperial College London, United Kingdom

The authors have indicated they have no financial relationships relevant to this article to disclose.

<table>
<thead>
<tr>
<th>What’s Known on This Subject</th>
<th>What This Study Adds</th>
</tr>
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<tbody>
<tr>
<td>Data obtained in adults indicate that even short-term hypothermia may have an effect on the metabolism of major analgesics and other drugs. No data are available for neonates concerning the impact of hypothermia on the pharmacokinetics of morphine.</td>
<td>The aim of our observational study, therefore, was to investigate whether morphine pharmacokinetics are altered during prolonged moderate systemic hypothermia in asphyxiated neonates, resulting in excessively high morphine concentrations compared with infants kept at normothermia; this would be important information for clinicians wishing to provide hypothermia.</td>
</tr>
</tbody>
</table>
Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure
DEVELOPMENTAL PHARMACOLOGY

PATTERN RECOGNITION

EXTRAPOLATION OF COMMON PATHWAYS
Take home message 2

To err is human
To repeat each other errors is stupid

common sense
good clinical practice

GETTING THE DRUG IN THE PATIENT
PK SAMPLING
Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls

SM Abdel-Rahman\textsuperscript{1,2}, MD Reed\textsuperscript{3,4}, TG Wells\textsuperscript{5,6} and GL Kearns\textsuperscript{1,2}
Study design: In this phase II protocol, the test article was prepared for administration by emptying the contents of the commercially available capsule into a plastic cup containing either apple juice or infant formula. At the time of data analysis, it became apparent that the cohort of children receiving apple juice demonstrated an increase in apparent oral clearance of the drug. This observation was identified to be putatively mediated by an interaction between apple juice and the transporter responsible for intestinal translocation of the drug, thus restricting oral bioavailability.

Undesired outcome: The alteration in presystemic clearance contributed by apple juice necessitated that a multiple-crossover bioequivalence bridging study be conducted in adults. The sponsor incurred the considerable expense nested in such a study and experienced a substantial delay in implementing the pediatric study plan for their drug.
**Study design:** In this phase II investigation, where the eligible age range spanned infancy through adolescence, the protocol allowed the tablet to be administered whole or crushed into pudding. As would be predicted, there was a significant difference in age by tablet integrity with older children preferentially swallowing the tablet and younger children preferentially receiving the crushed dose.
Study design: This phase II investigation was designed to determine the pharmacokinetics of an anti-infective agent in a population of children. Varied options for dose administration were afforded by the protocol depending on patient age. Children who were capable swallowed the proprietary tablet, whereas those unable to swallow the solid formulation received an oral suspension developed by the sponsor. The tablet was well tolerated in all children; however, a substantial number of children receiving the suspension vomited their dose.

Undesired outcome: This unsatisfactory tolerability profile placed the sponsor in a position of having to reformulate their oral suspension before marketing. The time and resources required for reformulation resulted in a considerable reinvestment of R&D costs for the sponsor and a delay in the release of their pediatric formulation.
**Study design:** A fixed weight-normalized (mg/kg) dose of drug was to be administered to young infants followed by a minimal pharmacokinetic sampling strategy. Given the absence of a suitable pediatric formulation, the institutional pharmacy at the study site was tasked with preparing the study drug. The adjacent figure illustrates $C_{\text{max}}$ values that were obtained in children receiving a dose from the first two batches of study drug. Notably, peak plasma concentrations were two-thirds lower for children receiving a dose from the second batch of drug than the first. High-performance liquid chromatography analysis of the compounded oral solution revealed that the drug concentration in batch two was 33% of nominal.

**Undesired outcome:** The children receiving a dose from batch two demonstrated post-peak concentrations that were below the limit of detection and the investigator was unable to determine their pharmacokinetic parameters. Although real-time analysis of the plasma concentrations allowed the investigators to detect the problem during the course of the investigation, this did not occur before more than 10% of total enrolled subjects were dosed from this batch. Notably, all subsequent batches employed in this study underwent high-performance liquid chromatography assay (at "unbudgeted" cost to the investigator) to verify accurate preparation before administration to study subjects.
<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Normal daily fluid requirement (ml)</th>
<th>Circulating blood volume (ml)</th>
<th>Maximum allowable sample volume over 2 weeks (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonate</td>
<td>1.5</td>
<td>144</td>
<td>120</td>
<td>3.6</td>
</tr>
<tr>
<td>Full-term neonate</td>
<td>4</td>
<td>384</td>
<td>144</td>
<td>9.6</td>
</tr>
<tr>
<td>Infant (3 years)</td>
<td>15</td>
<td>1,250</td>
<td>320</td>
<td>36</td>
</tr>
<tr>
<td>Child (12 years)</td>
<td>40</td>
<td>1,920</td>
<td>1,200</td>
<td>96</td>
</tr>
</tbody>
</table>
Mind numbing: Anesthesia in baby rats stunts brain development.

Common general anesthetics given at an early age may cause brain damage and other neurologic problems.
Maximal effect in rats: 6-9 days (Anand & Scalzo 2000)

No effect in rats: 14 days (Ruda et al. 2000)

Rat - Human
0 day - 24 wks GA
7 days - full-term
14 days - 1-year-old

Children differ

The concept of best attempt/guess

Multidisciplinary approach