A Knowledge of Pharmacology Improves Outcome in Children

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A Lack of Knowledge of Pharmacology Leads To Bad Outcomes in Children

Paediatric anaesthesia morbidity and mortality has historically been highest in 0-1 year age group

Some of this increased morbidity and mortality is attributable to poor understanding of

- drug effects (pharmacodynamics) that change with age
- maturational changes in the way the body handles a drug (pharmacokinetics),
- adverse effects that are age specific
Halothane absorption

Fig. 2. Halothane equilibration curves. The two lower curves were obtained in adult studies; the lowest from Salanitre et al., figure 3,* the other adult curve from data by Sechzer et al.⁷

Halothane MAC
Bradycardia at induction <1 year of age

- morbidity
  - hypotension (32%), asystole/VF (14%), death (8%)
- halothane 35%, hypoxia (22%)
- ASA status, emergency
- qualification anaesthetist & arrest
  - non-paediatric trained 19/10,000
  - paediatric anaesthetist 0/10,000 Keenan 1994
Cytochrome P450 maturation (Phase 1)

• Immature at birth
• Different CYPs mature at different rates

Practical Implication

• Reduce Infusion rates in neonates
  – Concentration = infusion rate/CL

  – Bupivacaine (CYP1A2)
  – continuous epidural infusion rates in neonates (0.2 mg/kg/h) are less than children (0.4 mg/kg/h)

Berde C. Anesth Analg 1992
What do we want to know to determine dose?

- Concentration-response relationship (PD)
- Target effect
- Target concentration
- Dose to achieve concentration (PK)
- Covariate effects
  - age, weight, disease
- Toxicity data

Anderson BJ. Pediatr Anesth 2012
Differences in the young

• **Size**
  – Smaller
    • Distances shorter, faster BMR, faster onset time
    • Increased metabolism (per kilo)

• **Maturation**
  – Body composition changing (V)
  – Drug metabolism immature (CL)
  – Response to drugs different

• **Toxicity**
  – Short term (e.g. verapamil and arrest)
  – Long term (e.g. tetracycline and teeth)
The Major PK Covariates in Children

• SIZE
• AGE
• Organ Function
• Body Composition
• Drug interactions
• Pharmacogenetics
• Environmental factors
• Circadian rhythms
Clearance changes with weight

- Allometric 3/4 power
- BSA (allometric 2/3 power)
- Per kilogram

[Graph showing the relationship between clearance and weight with different power laws]
Allometric Examples


Initial Dose or Infusion

**Bolus Dose**

Dose = $V \times \text{Target Concentration}$

**Infusion**

At steady-state

Rate in = Rate out

Infusion rate = $CL \times \text{Target Concentration}$
Clinical Considerations

- **Propofol Infusion**
  - Adult: bolus 1 mg/kg then 10-8-6 mg/kg/h
  - Child: bolus 1 mg/kg then 15-13-10 mg/kg/h

Mani V. Pediatr Anesth 2010
Clearance changes with weight

Maturation

- Allometric 3/4 power
- BSA (allometric 2/3 power)
- Per kilogram
Renal and Metabolic Maturation

Propofol
TM$_{50}$ 38.5 weeks
Hill 4.6

GFR
TM$_{50}$ 47.6 weeks
Hill 3.4

Morphine
TM$_{50}$ 54.2 weeks
Hill 3.92

Paracetamol
TM$_{50}$ 52.2 weeks
Hill 3.4

Dexmedetomidine
TM$_{50}$ 46.5 weeks
Hill 2.78

Propofol Metabolism
Glucuronide
CYP2B6, CYP2C9 or CYP2A6

Maturation of hepatic enzyme activity
Caffeine - a long acting stimulant in neonates

- Good central respiratory stimulant
- Poor hepatic clearance: Immature P450 CYP1A2
- Immature renal clearance
- T1/2 days in neonate, hours in adults
Caffeine half-life changes with age

## Onset Time of Drugs
e.g. atracurium

<table>
<thead>
<tr>
<th>Age Group</th>
<th>wt (kg)</th>
<th>Onset time (min)</th>
<th>Onset time std (min/70kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neonate &lt;1mo</td>
<td>3.5</td>
<td>1.4</td>
<td>2.96</td>
</tr>
<tr>
<td>infant &lt;1yr</td>
<td>7</td>
<td>1.7</td>
<td>3.02</td>
</tr>
<tr>
<td>child 3-10yr</td>
<td>25</td>
<td>2.3</td>
<td>2.97</td>
</tr>
<tr>
<td>adult</td>
<td>70</td>
<td>2.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Anderson CPK 1997
The Link Parameter

Elimination half-time
\[ T_{1/2} = \frac{\ln(2)}{K_{e0}} \]

Central V1 (L)

Peripheral V2 (L)

Drug in

Q (L.min\(^{-1}\))

K21 (min\(^{-1}\))

K12 (min\(^{-1}\))

Central V1 (L)

K1e (min\(^{-1}\))

Effect Compartment

K10 (min\(^{-1}\))

CL (L.min\(^{-1}\))

EFFECT

K_{e0} (min\(^{-1}\))
Equilibration Rate Constant and Time to Peak in Children

\[ k_{e0\text{ Propofol}} = 1.03e^{-0.12\text{ age}} \]
\[ R^2 = 0.44 \]

\[ T_{\text{peak Propofol}} = 0.14\text{ age} + 2.08 \]
\[ R^2 = 0.27 \]
Effect compartment concentrations are dependent on the estimate for the equilibration half-time (T1/2keo)

Simulated plasma time-concentration profiles for a typical 20 kg child and a 2.9 kg neonate.

PK parameter estimates from Kataria and Allegaert.
Body Composition

• Total body water and ECF are increased in neonates

• Fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4-5 months of age.

• “Baby fat” is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult)

• Reduced binding proteins e.g. AAG

• Spinal column takes greater proportion body mass
Body Water

PERCENT OF BODY WEIGHT

TBW

ECW

FETUS

CHILD

ADULT

months

years

Friis-Hansen  Acta Paediatrica 1954
Neuromuscular Blocking Drugs

• ↓ Sensitivity neuromuscular junction
  – Fetal neonatal postjunctional acetylcholine receptors differ from adults receptors (γ-subunit instead of an ε-subunit)

• ↓ Quantal release acetylcholine

• ↑ Vd → initial dose is same in neonates and adults

• Duration of effect longer in neonates
  – Clearance reduced
Vecturonium ED$_{95}$

- 47 SD 11 mcg/kg in neonates and infants
  - Immature NM Junction
- 81 SD 12 mcg/kg in children 3 - 10 years
- 55 SD 12 mcg/kg >13 years
  - The reason for the larger dose requirement in children compared with adults is unclear but it be the result of increased muscle bulk.

(Meretoja O. Anesth Analg, 1988:67;21-6)
Protein binding - AAG

- Alpha-1 acid glycoprotein reduced in neonates
- Bupivacaine is bound to AAG

Bolus epidural dose of bupivacaine in neonates is lower than in children (1.5-2 mg/kg vs. 2.5 mg/kg) because a greater proportion will be unbound drug and it is unbound drug that exerts effect

Booker P. Br J Anaesth 1996
Preterm and full-term infants have a much greater CSF volume relative to weight than a child (4 ml/kg in children < 15 kg) or adult (2 mg/kg). This may account in part for the increased dose (mg/kg) of local anesthetic required in infants to produce a successful subarachnoid block. Duration of blockade is shorter in neonates and this may be due to a higher CSF turnover rate than adults.
Is It Just Pharmacokinetic?

Central V1 (L) → Peripheral V2 (L)

Drug in

Q (L.min⁻¹)

K21 (min⁻¹)

K12 (min⁻¹)

Central V1 (L) → Effect Compartment

K₁e (min⁻¹)

K₁₀ (min⁻¹)

CL (L.min⁻¹)

Kₑ₀ (min⁻¹)

EFFECT (Pharmacodynamics)

Effect = \( \frac{E \text{ max} \cdot C_N}{EC_{50}^N + C_N} \)
Age & Altered Pharmacodynamics

• Bronchodilators
  – smooth muscle ↓
• Warfarin
  – sensitivity ↑
• Cyclosporin (immunosuppression ↑)
• Midazolam
  – ↑ GABBA$_A$ receptor, ↑ Blood flow
• Calcium and neonatal heart
• Gastric prokinetics
  – ↓ sensitivity
Paracetamol PK & PD Variability

Anderson BJ Eur J Pharmacol 2001
The Anaesthetic Solution to Variability

- clinically used doses of succinylcholine (1.0-1.5 mg/kg) are equivalent to 3-5 times the ED90
- explain the excellent intubating conditions provided by this drug

- Smith CE. Anesthesiology 1988
The Pharmacological Solution to Variability

- The Holy Grail of clinical pharmacology is prediction of drug PK and PD in the individual patient
- This requires knowledge of the covariate effects that contribute to variability

Age and Isoflurane MAC

Reason uncertain

↑ cerebral blood flow
↑ GABA<sub>A</sub> receptor numbers
Shifts in the regulation of chloride transporters

LeDez K. Anesthesiology 1987
ORIGINAL ARTICLE


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What do we want to know to determine dose?

Pharmacokinetics
Pharmacodynamic
Adverse Effects
Propofol Toxicity in Neonates
- an immediate effect

- Neonatal data from neonatologists
  - Papoff P. Pediatrics 2008; 121:448-9
  - Ghanta S. Pediatrics 2007; 119:e1248-e1255

- Concerns BP

- Editorial
Neonatal Hypotension With Propofol 3 mg/kg

Remifentanil infusion in children

- Use adult parameter estimates
  - Minto C. Anesthesiology 1997; 86:10-23
- Remifentanil V & CL decrease with age
  - Increases safety
- Short half-life augments safety
- Target plasma rather than effect compartment

- Covariate effects
  - hypothermia ↓CL, post CPB ↑CL

Standing J. Pediatr Anesth 2010
Neurosurgical children
Ketamine (and other anaesthetic drugs) and the neonate - a long term effect

Concerns about widespread neuronal apoptosis and long-term memory deficits

Other long term effects due to impact at critical time:

- Thalidomide - phocomelia
- Stilboesterol - vaginal carcinoma
- Tetracycline - teeth staining
Idiosyncratic Drug Reactions and Pharmacogenomics

- Simvastatin and muscular damage
  - Xome 12

- Flucloxacillin and hepatic injury
  - 8/100,000
  - Xome 6