Pharmacokinetic and Pharmacodynamic Considerations in Infants and Neonates

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Disclaimer

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Outline

• Dose selection in neonates and infants
• Impact of development on PK
  – Impact of growth and maturation
  – Pharmacogenetics
  – Treatment modalities/organ dysfunction
• Impact of development on PD in neonates and infants
Neonatal and Infant dosing

- Goal for dose selection in neonates/infants:
  - Target effect (PD)
  - Understanding of concentration response to predict target concentration
  - Dose to achieve concentration (PK)
  - Understand sources of **inter and intra**-patient variability in PK and PD
Major sources of PK variability infants and neonates

**Neonates/infants**
- **AGE** (maturation)
- **SIZE** (growth)
- Organ function
  - Pathological processes (e.g. sepsis)
  - Tx modalities (eg. ECMO)
- Pharmacogenetics

**Older children**
- **SIZE**
- Organ function
- Pharmacogenetics
Developmental impact on PK: Growth

- Order of magnitude difference in BW
  - 1 order of magnitude difference just in neonates (0.5-5kg)
  - Even greater difference between neonates/infants and adults (0.5-50kg)

- Non-linear relationship with body size and metabolic processes (GFR, drug metabolism)
  - Dosing cannot be scaled down directly from dosing in adults using body weight (Dose too small in infants and too large in neonates)

Morphine dose to achieve 10mcg/ml
- highest in 1-3 y/o and decreasing until adult rates in adolescents;
- impact of maturation in neonates and young infants
Development Impact on PK Maturation

• Age: surrogate for maturation in infants and neonates
  – GA: maturation before birth
  – PNA: maturation after birth
  – PMA: maturation before and after birth

PK parameters may need to be described as a function of both age and related to body weight
  • Clearance of many drugs can be described using PMA

Anderson et al. 2009
Absorption

• Oral absorption
  • **Slower rate of absorption:**
    • Prolonged gastric emptying time (e.g. phenobarbital)
  • **Lower drug absorption for some lipophilic drugs**
    • Immature biliary function and activities of pancreatic enzymes (e.g. erythromycin)
  • **Altered bioavailability**
    • Altered stability due to higher gastric pH:
      • ↑ Fa for acid labile drugs (ampicillin, erythromycin, amoxicillin)
    • Altered degree of ionization due to higher gastric pH:
      • ↓ Fa due for weak acids (phenobarbital, phenytoin): may require ↑ loading doses
    • Altered intestinal metabolism due to lower intestinal enzyme activity/transporters:
      • ↑ Fa for some drugs (midazolam)

• Percutaneous absorption
  • **Increased bioavailability of some drugs**
    • ↑ hydration of epidermis, greater perfusion of subcutaneous layer, and ↑ BSA:body mass ratio (e.g. topical steroids)
Distribution

• Vd determines loading dose and half-life
  – ↑ Vd when extensive drug distribution to tissue
  – ↓ Vd when high plasma concentration
  – Determined by:
    • Tissue binding
    • Plasma protein binding
    • Hydro/lipophilicity of drugs
Distribution: Body composition

- Age related changes in body composition:
  - TBW:
    - ~80% in newborns to 60% by 1 yr
  - Body fat:
    - 1-2% in preterm, 10-15% in term neonates, and 20-25% in 1 yr olds

- Impact on PK depends on physicochemical properties of drugs
  - Hydrophilic drugs: ↓plasma conc due to ↑ Vd (e.g. gentamicin)
  - Lipophilic drugs: may have ↑ plasma conc due to↓ Vd (e.g. diazepam)
Extrapolation of E-R (total drug con) data from adults/older children is difficult for drugs with ↑ protein binding:

• Lower protein binding in neonates/infants:
  — Lower circulating levels:
    • Albumin levels are directly proportional to GA
    • α-1-acid glycoprotein levels 50% of adult values in neonates
  — Lower binding affinity
  — High concentrations of endogenous competing substrates (free fatty acids, bilirubin, fetal albumin)

• Lower protein binding may result in:
  — Increased distribution of drugs from plasma to tissues (e.g. phenobarb)
  — Higher concentration of fraction unbound in plasma (e.g. micafungin, phenytoin); interpretation of total plasma level difficult

Altered safety:

• Lower protein binding affinity: Drugs can compete and displace bilirubin from binding
  — Results in increased levels of unconjugated bilirubin and risk of kernicterus in neonates (e.g. ceftriaxone)
Distribution: CNS

- The ability of anti-infectives to enter the CNS depends on:
  - The intracranial compartment of interest
  - Molecular size, electric charge, lipophilicity, plasma protein binding, affinity to active transport
  - Host factors e.g. meningeal inflammation and CSF flow

- Extrapolation of CSF-to-serum concentration ratio to neonates/infants from data in adults/older infants is difficult:
  - Limited data on ontogeny; available data mostly from nonclinical studies
  - Blood Brain Barrier (BBB): less myelination and immature in newborns
    - ↑ permeability to drugs (e.g. phenobarbital; amphotericin B)
  - Limited P-gp expression in brain at birth
    - Increases postnatal and reaches adult levels at ~3–6 m/o of age
    - Decreased drug efflux back to systemic circulation (e.g. morphine)
  - Pathologic conditions
    - Can release chemical mediators that increase BBB permeability (e.g. sepsis & endothelin-1, TNFα)
    - Hypoxia/ischemia can disrupt tight junctions and increased BBB permeability (mediated by cytokines, VEGF, and NO?)
Metabolism

• Liver drug metabolism:
  – Phase I: Decrease lipophilicity and enhance renal excretion; majority mediated by cytochrome P450 (CYP) enzymes
  – Phase II: Conjugation of a functional group on a molecule with hydrophilic endogenous substrates (e.g. glucuronidation, sulfation, acetylation)

• Other sites: kidney, intestine, lung, and skin
Metabolism: Phase 1

Delayed maturation of CYP enzymes contributes to variability in drug clearance under 2 yrs:

- Unique pattern of maturation for each enzyme system
- Activity of enzymes increases in a nonlinear manner with age
- By 1-2 yrs, most isoenzymes reach adult values

H Lu et al. JPPT 2014
Metabolism: Phase 1

- CYP 3A7: Primary isoenzyme expressed during prenatal period
  - Detectable as early as 50 to 60 days gestation
  - Declines rapidly after birth to non-detectable levels by 1 yr of age
  - Not present in extrahepatic tissues
  - Lower metabolic capability for CYP3A7 compared to CYP3A4

H Lu et al. JPPT 2014
Metabolism: Phase 2

- Phase 2 enzymes
  - Glucuronidation ~ 15% of drugs metabolized (e.g. acetaminophen, morphine)
  - Limited data on developmental changes
    - Sulfate conjugation is pronounced in neonates
    - Glucuronidation is deficient in neonates and infants
    - May alter the relative contribution of each enzyme resulting in differences in the relative metabolite concentrations
  - Nonlinear relationship between clearance and age similar to phase 1 enzymes
  - By 1-2 yrs, most reach adult values

Morphine clearance changes with age

Anderson B et al. Anesthesiology 2002
Metabolism: Transporters

• Transport-mediated uptake of drugs into hepatocytes and efflux into the bile
  – Limited data on ontogeny of P-gp in humans
    • low at birth and increases during 1st few months of life, reaching adult values by 2 yrs
  – Limited data on clinical significance of developmental changes of transporter function
Metabolism: Genetic Polymorphism

In addition to size and maturation, polymorphism may impact drug clearance

- **Extrapolation of adult observations may not apply**
- May contribute to inter-individual variability when isoenzyme active in early life (e.g. tramadol and CYP2D6; isoniazid and NAT2)
- **Less impact on clearance if isoenzymes are not sufficiently active** (e.g. ibuprofen and CYP2C8 and CYP2C9)

Both PMA and CYP2D6 polymorphisms determine Tramadol O-demethylation in neonates/infants

Simultaneous contribution of PMA and CYP2D6 activity score on the 24 urine log, M/M1 values

Allergart K et al. 2008
Renal Elimination

- Renal elimination
  - Dependent on glomerular filtration, tubular excretion and tubular reabsorption
- GFR: Maturation varies with degree of prematurity and PNA reaching adult values by 1 yr of age
- Tubular secretion: 20-30% at birth and matures by 15 months
- Tubular reabsorption: Reaches adult values by 2 yrs

Rhodin et al. Pediatric Nephrology, 2009
Pharmacodynamics

- Limited data on receptor expression and sensitivity
- Differences can alter exposure response relationship in neonates and impact safety and the ability to extrapolate efficacy data from older children and adults
  - GABAA receptors with age-dependent function in brain: Excitatory effects in neonates/infants; Inhibitory effects in older children/adults
  - Vit K dependent factors (II, VII, IX, X): ~50% of adult values in newborns
  - Immature immune response in neonates/infants
- For anti-infectives, developmental changes are not expected to impact PD response when the disease is similar to older children and adults but may impact safety (e.g. nephro or ototoxicity of aminoglycosides)
Impact on PK/PD in neonates/infants

• Treatment modalities
  – ECMO
    • Altered volume of distribution
    • Higher clearance due to adsorption in the ECMO circuit (lipophilic drugs e.g. fentanyl, propofol)
  – Hypothermia
    • Reduced clearance for some drugs (e.g. morphine, phenobarbital)
    • Impact of PK/PD relation of antibiotics in neonates?

• Diseases/conditions
  – Sepsis
  – Renal failure
Summary

• Developmental changes contribute to age-related changes in absorption, distribution, metabolism and elimination.
• Growth and maturation are the most important determinants of variability in PK in infants and neonates.
• Extensive information exist on maturational PK for **INITIAL PK** prediction/dose estimation in neonates/infants.
• Current gaps in our knowledge include impact of maturation on:
  – Drug distribution to the CNS in early life
  – Pharmacodynamics and receptor function
  – Disposition of therapeutic proteins
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