Pharmacokinetic and Pharmacodynamic Considerations in Infants and Neonates

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Disclaimer

- The views and opinions expressed in this presentation reflect those of the presenter and do not necessarily reflect the views and opinions of the U.S. Food and Drug Administration.

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

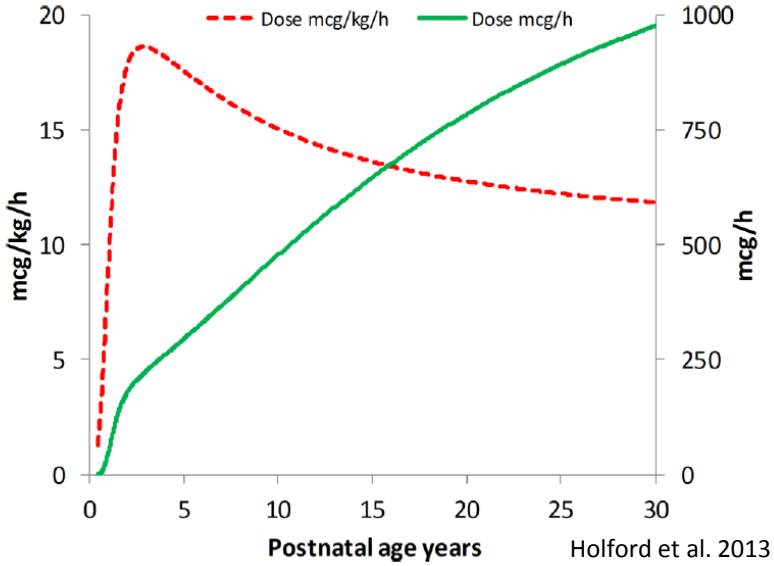
Older children

- **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 btwn 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



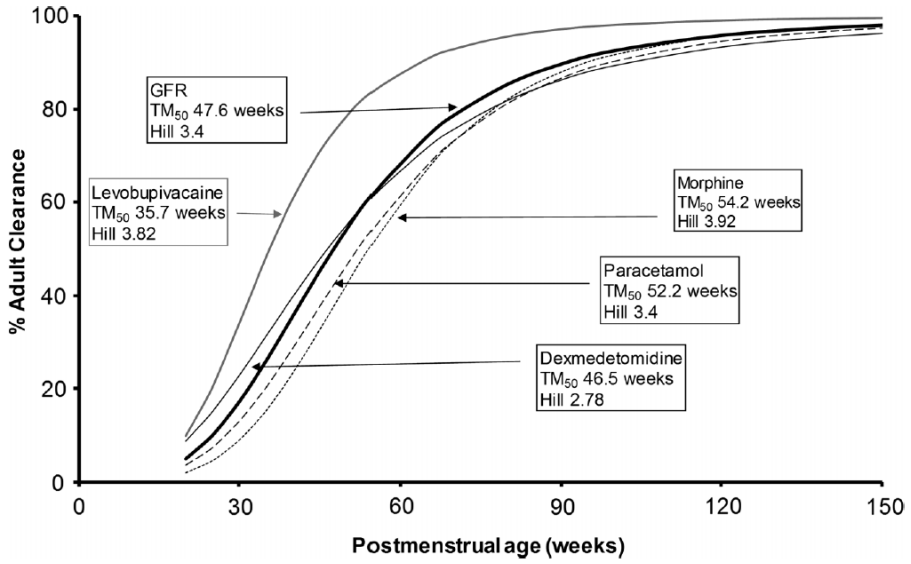
Holford et al. 2013

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

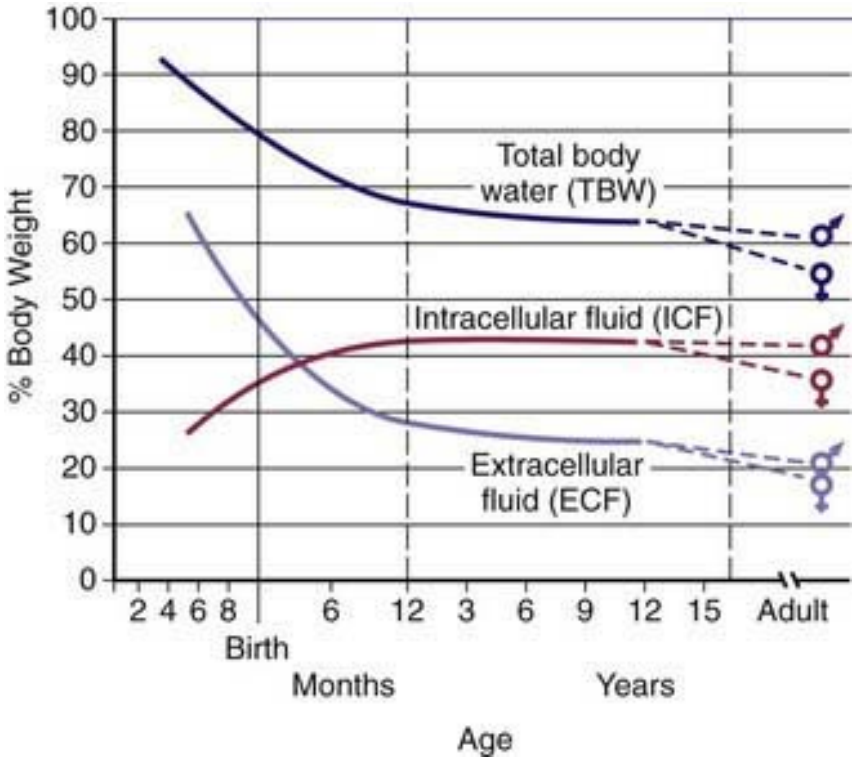
- Oral absorption
  - **Slower rate of absorption**:
    - Prolonged gastric emptying time (e.g. phenobarbital)
  - **Lower drug absorption for some lipophilic drugs**
    - Immature biliary function and activities of pancreatic enzymes (e.g. erythromycin)
  - **Altered bioavailability**
    - Altered 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)



Winters. The body fluids in pediatrics. 1973

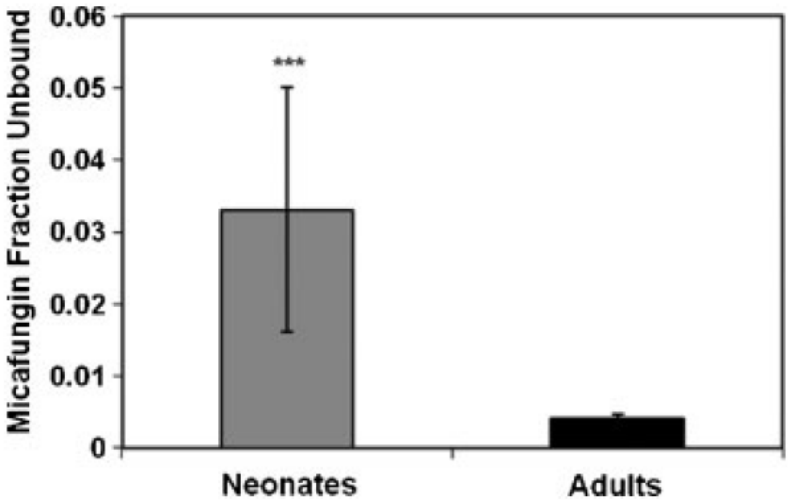
Distribution: Plasma Protein binding

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)



Yanni, Souzan B., et al.. 2011

Micafungin fraction unbound significantly higher in neonates compared with adults

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?)

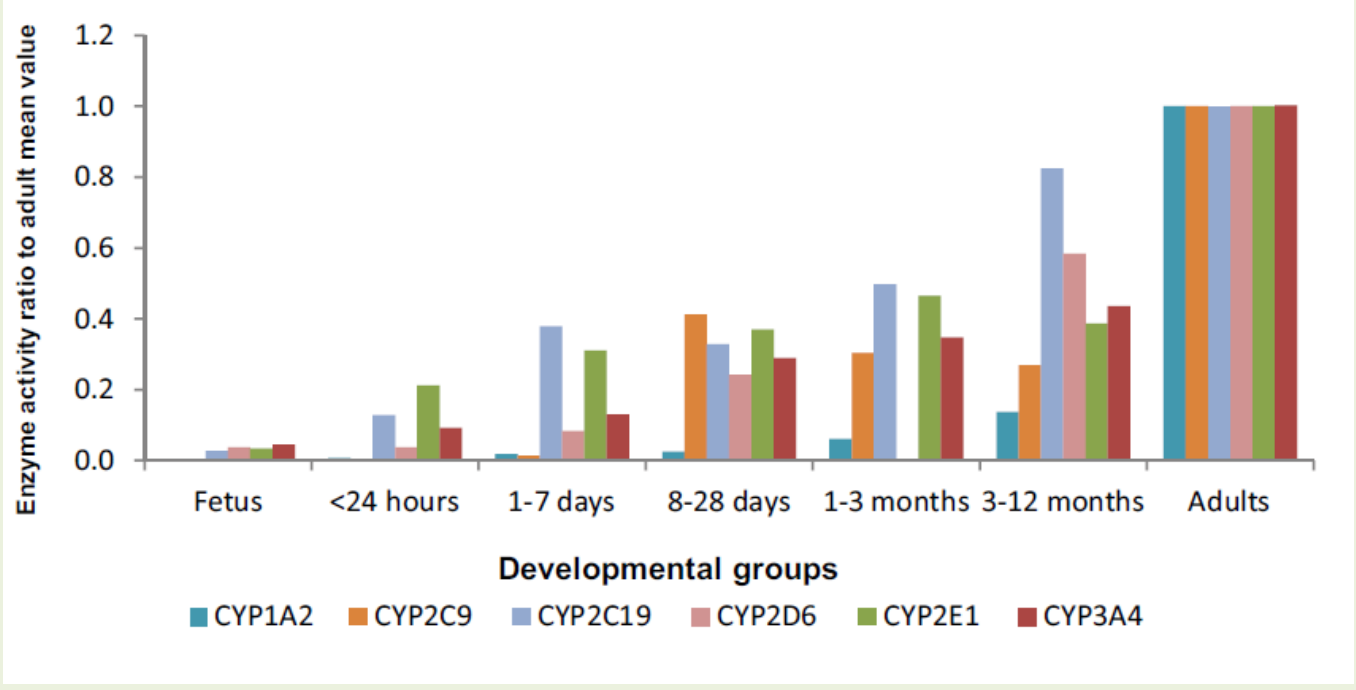
Metabolism

- 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:

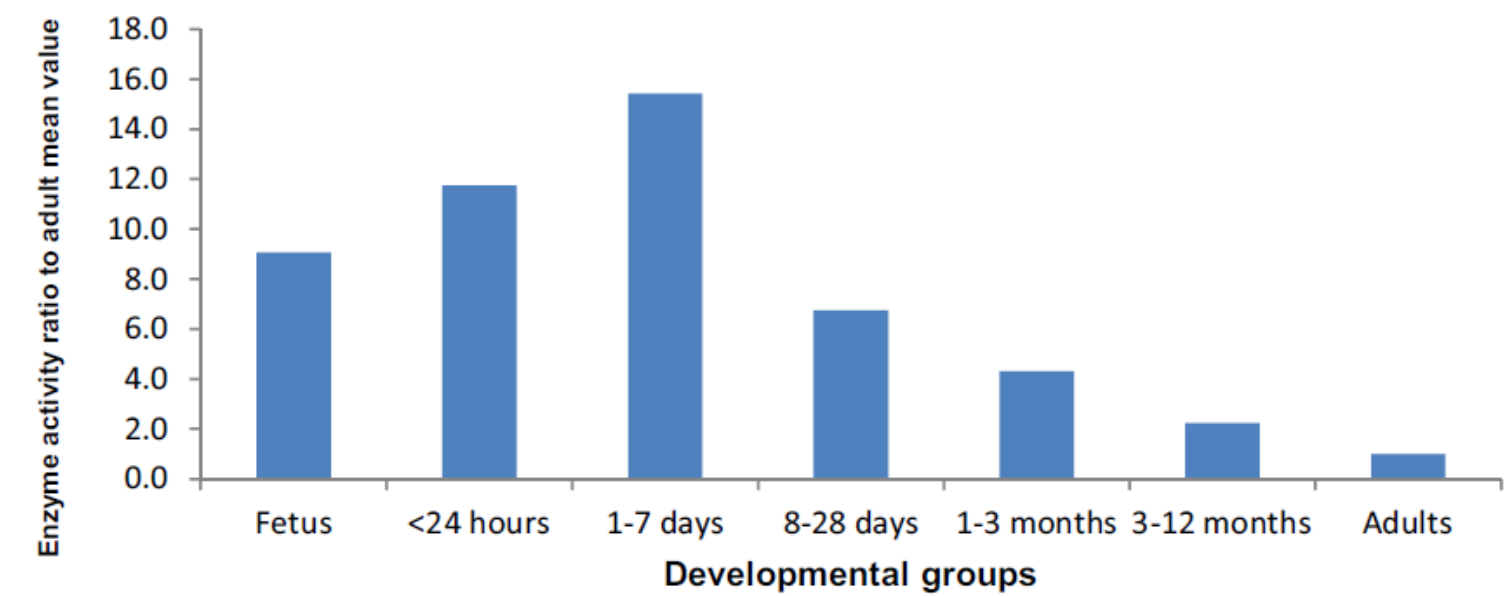
- Unique pattern of maturation for each enzyme system
- Activity of enzymes increases in a nonlinear manner with age
- **By 1-2 yrs, most isoenzymes reach adult values**



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**

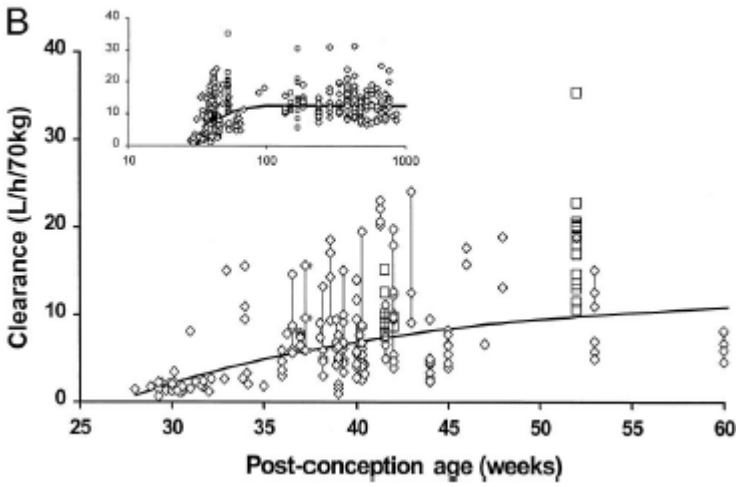


H Lu et al. JPPT 2014

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

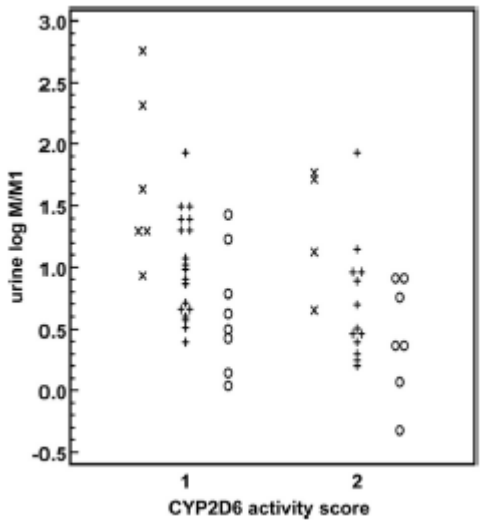
- Transport-mediated uptake of drugs into hepatocytes and efflux into the bile
  - Limited data on ontogeny of P-gp in humans
    - low at birth and **increases during 1st few months of life, reaching adult values by 2 yrs**
  - Limited data on clinical significance of developmental changes of transporter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



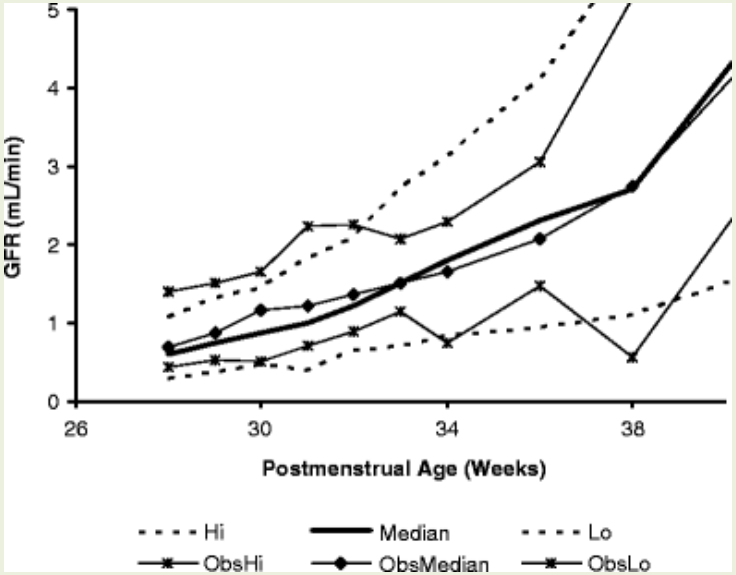
X: less than 37 wk PMA
+: 37-41 wk PMA
o: 41 wk PMA

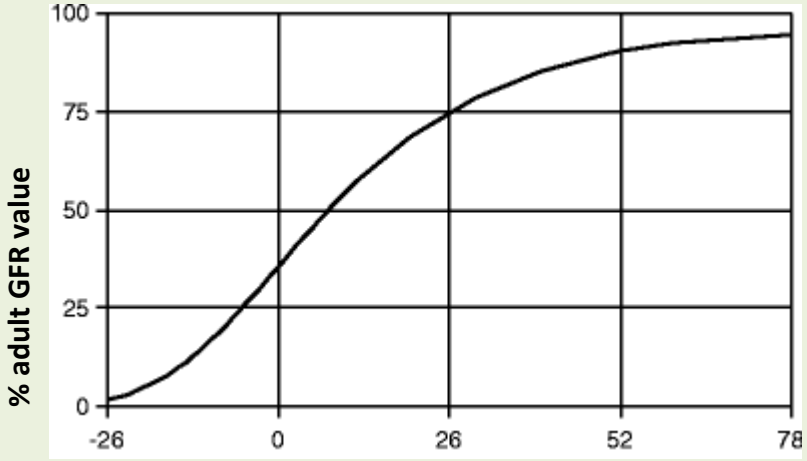
Allergart K et al. 2008

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

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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