Developmental pharmacology of analgesics

Christopher McPherson, PharmD
Clinical Pharmacist, Neonatal Intensive Care Unit, St. Louis Children’s Hospital
Associate Professor, Department of Pediatrics, Washington University School of Medicine
Disclosure statement

• I have no financial interests or conflicts of interest with any pharmaceutical company to disclose relating to this presentation

• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies
Absorption


Distribution

Metabolism – Phase I

CYP 3A
CYP 1A2
CYP 2C19
CYP 2C9
CYP 2A6
CYP 2B6 and 2D6
CYP 1E2

Metabolism – Phase II

A. UGT1A1

B. UGT1A3

C. UGT1A4

D. UGT1A6

E. UGT1A9 (propofol)

F. UGT1A9/2B7 (Mycophenolic acid)

G. UGT2B4 *

H. UGT2B7

I. UGT2B10

Excretion

Opioid metabolism

- Morphine
  - Morphine-3-glucuronide (Glucuronidation by UGT 2B7)
    - Urinary excretion
  - Morphine-6-glucuronide (Glucuronidation by UGT 2B7)
    - Urinary excretion
  - Morphine-3-6-diglucuronide
    - CYP 3A4
    - Urinary excretion
  - Normorphine
    - Urinary excretion
  - Morphine-3-ethereal sulfate

- OCT-1 uptake
  - ~90%
  - ~10%
Ontogeny of morphine elimination pathways

Ontogeny of morphine elimination pathways

Serum opioid concentrations may not reflect CSF concentrations

Opioid receptor ontogeny

μ-opioid receptor expression in rat dorsal root ganglion

Opioid responsive cells in rat dorsal root ganglion

Opioid receptor ontogeny

Adult rat dorsal root ganglion
(MOR positive small and medium cells)

Neonatal rat dorsal root ganglion
(Diffuse distribution of MOR positive cells)

Opioid receptor ontogeny

Decreased morphine sensitivity with age in the setting of mechanical stimulation

No difference in morphine sensitivity with age in the setting of thermal stimulation

Developmental impact

25 week

30 week

33 week

Term equivalent (37-40 weeks)

Adult

Term control
Morphine exposure significantly associated with poorer motor scores (p<0.001) and cognitive outcomes (p=0.006) at 18 months CA

Mediates association with anxiety/depression

Mediates association with acting out


Morphine pharmacokinetics in therapeutic hypothermia

Opioid metabolism

Morphine

- Morphine-3-glucuronide
  - Glucuronidation by UGT 2B7
  - OCT-1 uptake
  - Urinary excretion
- Morphine-6-glucuronide
  - Glucuronidation by UGT 2B7
  - Urinary excretion
- Morphine-3-6-diglucuronide
  - Morphine-3-ethereal sulfate
  - Normorphine
  - Urinary excretion

Fentanyl

- CYP 3A4 N-dealkylation
- Norfentanyl
  - Urinary excretion
Ontogeny of major hepatic CYP enzymes

CYP 3A
CYP 1A2
CYP 2C19
CYP 2C9
CYP 2A6
CYP 2B6 and 2D6
CYP 1E2

Fentanyl pharmacokinetics in preterm neonates

Developmental formulations

- \(1 \text{ mcg/kg} \times 1 \text{ kg} \div 50 \text{ mcg/mL} = 0.02 \text{ mL}\)
- \(1 \text{ mcg/kg} \times 1 \text{ kg} \div 5 \text{ mcg/mL} = 0.2 \text{ mL}\)

Acetaminophen metabolism

- **Acetaminophen**
  - Glucuronidation by UGT-1A6 (~55%)
  - CYP 2E1 (~10%)
  - Sulfation by SULT 1A1, 1A3/4, and 1E1 (~30%)
- **NAPQI**
  - Glutathione conjugation
  - Cysteine + Mercapturic acid
    - Urinary excretion (~10%)
- **Acetaminophen glucuronide**
  - Urinary excretion
- **Acetaminophen sulfate**
  - Urinary excretion
Ontogeny of acetaminophen elimination pathways in VPT neonates
Ontogeny of acetaminophen elimination pathways

Ontogeny (developmental stages) of acetaminophen metabolism:

- **Neonatal (0 to 27 days):**
  - SULTs 63%
  - UGTs 29%
  - Other 6%
  - CYPs 2%

- **Infancy (28 to 364 days):**
  - SULTs 58%
  - UGTs 31%
  - Other 6%
  - CYPs 5%

- **Early childhood (1 to <6 years):**
  - SULTs 59%
  - UGTs 27%
  - Other 6%
  - CYPs 8%

- **Adulthood (>18 years):**
  - SULTs 31%
  - UGTs 54%
  - Other 6%
  - CYPs 9%

Acetaminophen PD
Local anesthetics in brief

- Metabolism mediated by CYP enzymes, highly protein bound

0-1 month receiving 0.2 mg/kg/hr

1-12 years receiving 0.4 mg/kg/hr

We are close for some drugs, with a reasonable understanding of the ontogeny of distribution (including secondary sites), metabolism, elimination, and receptor expression.

My tentative conclusions

• We have made tremendous progress to understand the ontogeny of various systems impacting drug pharmacokinetics
  • Pharmacokinetic extrapolation across age groups is hindered by the importance of all aspects of developmental pharmacokinetics

• Larger gaps exist in our knowledge of effective site concentrations and receptor ontogeny.

• Different classes of drugs have different pitfalls.

• Both short-term and long-term safety studies are vital.
  • Formulation may influence short-term safety.