Common Medication in the NICU

Developmental Pharmacology

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What do These Picture Have in Common?

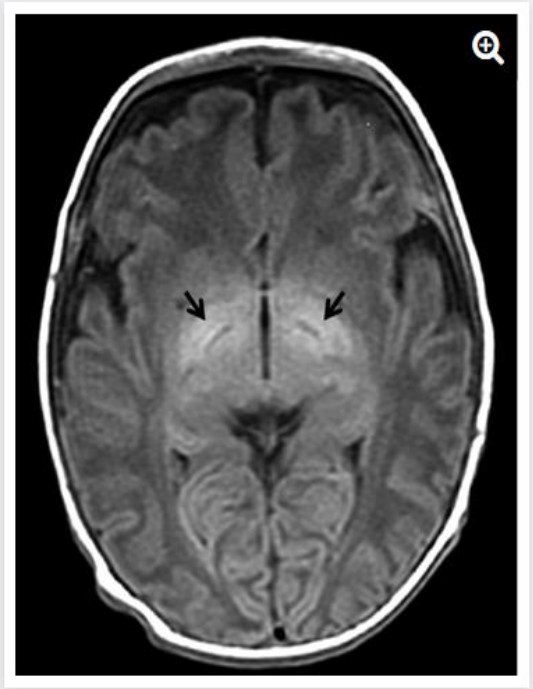
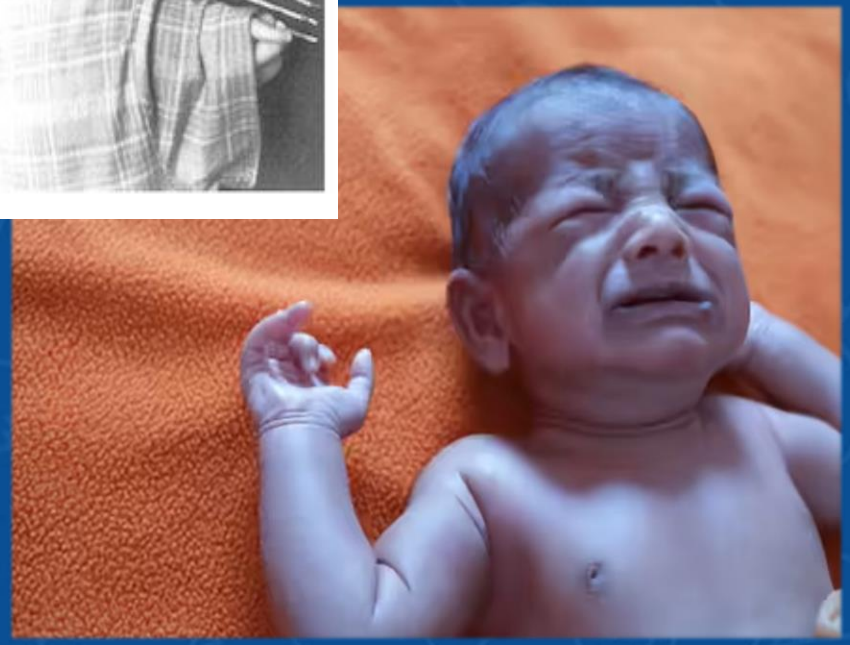


FIG 1.

Download figure | Open in new tab | Download powerpoint

Axial T1-weighted (TR/TE = 516/9) MR image shows abnormal hyperintensity in the globus pallidus (*arrows*) in an infant with kernicterus.



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Children are not little adults

"Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but…has its own independent range and horizon."

Dr. Abraham Jacobi, the Father of American Pediatrics

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Age Terminology During the Perinatal Period

- Gestational Age (GA)
  - ✓ Time elapsed between first day of the last menstrual period and the day of delivery
- Postnatal age (PNA)
  - ✓ Time elapsed since birth
- Postmenstrual age (PMA)
  - ✓ Gestational age plus chronological age

http://pediatrics.aappublications.org/content/114/5/1362.full.html

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Developmental Pharmacology (ADME)

- Absorption
- Distribution
- Metabolism
- Excretion

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Developmental Pharmacology (ADME)

- Absorption
  - GI
  - IM
  - Rectal
  - Topical
- Distribution
  - Total Body water
  - Proteins in the plasma
- Metabolism
  - Liver Function
- Excretion
  - Renal Function

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Neonatal Drug Absorption

- Oral Absorption
  - Gastric acidity – affects the stability and degree of ionization of a drug
    - In the neonatal period, intragastric pH is relatively elevated
      - Due to reduction in basal acid output and total volume of gastric secretions
      - Gastric pH slowly declines until it reaches adult values at about 2 year of age
    - Increase absorption of acid-labile drugs
    - Decrease absorption of weak acids
  - Gastric emptying is reduced
    - Decrease absorption
    - GA and PNA both affect gastric emptying rate with prolonged emptying times seen in premature infants
  - Intestinal transit time is relatively slower in neonates due to reduced motility and peristalsis

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Neonatal Drug Absorption

- Intramuscular Absorption
  - Absorption may be unpredictable and decreased
    - ❖ Reduced skeletal-muscle blood flow
    - ❖ Inefficient muscle contractions which is responsible for drug dispersion
    - ❖ Painful at injection site

- Rectal Absorption
  - Limited predictability in absorption
    - ❖ May have increase absorption due to blood supplies to the anus and lower rectum drain directly into the inferior vena cava which bypass the 1st pass metabolism
    - ❖ Increased contractions in the rectum which can enhance the expulsion of the solid forms of drug – effectively decreasing absorption

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Neonatal Drug Absorption

- Topical Absorption
  - Absorption is increased
    - ❖ Immature epidermis
      - › thinner stratum corneum, especially in the preterm neonate
    - ❖ Increased skin hydration
      - › greater cutaneous perfusion and hydration of the epidermidis relative to adult
    - ❖ Ratio to total body surface area to body mass in neonates and young children far exceed that in adults

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Neonatal Drug Distribution

- Total Body Water Content
  - 75% in neonates (approx. 80%-90% in preterm) vs. 60-65% in adults
    - ❖ Vd – measurement of the extent to which a drug will distribute in the intravascular compartment and migrate into the extravascular tissues
    - ❖ Hydrophilic drug has a large volume of distribution (Vd)
      - › Concentration is lower in neonates than adults when the same weight-based dose is given
    - ❖ Lipophilic drug has a small volume of distribution (Vd)
      - › Concentration is higher in the effect compartment when similar dose (mg/kg) is administered

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Neonatal Drug Distribution

- Protein Binding
  - Increase in available drug/free (unbound) drug
    - ❖ Fetal albumin
      - › Reduced binding affinity
    - ❖ Alpha-1 glycoprotein
      - › Low which allows more free drug availability
    - ❖ Competition for binding sites
      - › Increases circulatory concentrations of endogenous bilirubin and free fatty acids
      - › Displaces drugs from albumin binding sites

Neonatal Drug Distribution

- Protein Binding

	Neonates	Infant	Child
Total Protein	↓	↓	=
Albumin	↓	=	=
α_1-glycoprotein	↓	↓	=
Fetal Albumin	Present	Absent	Absent

Neonatal Drug Metabolism

- Hepatic Metabolism
  - Phase I Enzymes
    - ❖ Cytochrome P450
      - › Activity is reduced by 50% comparted to adult
      - › Activity increases with advancing GA and PNA
      - › Equivalent to adult capacities at 6 months of age
      - › CYP3A4 – is less than 10% of the activity in adults
      - › CYP1A2 – not even present until 1-3 months of age
      - › CYP2C9 – not fully active for the first 10 day of life

Neonatal Drug Metabolism

- Hepatic Metabolism
  - Phase I Enzymes: Cytochrome P450

Table 2. Selected Cytochrome P-450 Isoenzymes and Corresponding Substrates

CYP1A2	CPY3A4
Acetaminophen	Alfentanil
Caffeine	Carbamazepine
Theophylline	Cisapride
	Erythromycin
CYP2C9	Fluconazole
Ibuprofen	Itraconazole
Phenytoin	Ketoconazole
	Lidocaine
CYP2C19	Nifedipine
Diazepam	Midazolam
Omeprazole	Nifedipine

Reiter, PD. Neonatal Pharmacology and Pharmacokinetics. NeoReviews. 2002

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Neonatal Drug Metabolism

- Hepatic Metabolism
  - Phase II Enzymes
    - ❖ Glucuronidation
      - › Less is known but know to be reduced in neonates
      - › Similar to CYP enzymes - Activity increases with advancing GA and PNA

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Neonatal Drug Excretion

- Renal Function
  - Drug passes through the kidneys and may undergo glomerular filtration (GFR), tubular secretion, and reabsorption
  - Drugs that are mainly eliminated by renal excretion is highly dependent on renal function
    - ❖ Nephrons become functional at 8 weeks of gestation
    - ❖ Nephrogenesis is complete at 36 weeks of gestation
    - ❖ Premature neonates are more sensitive to nephrotoxic medications

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Neonatal Drug Excretion

- Renal Function
  - Reduced GFR
    - ❖ GFR rate achieves adult levels at the end of the first year of life
    - ❖ Term GFR is approximately 30% of adult GFR
    - ❖ At 48 weeks PMA – infants achieve 50% of adult GFR
  - Tubular secretion may play a role in drug clearance
    - ❖ Immature at birth until 1 year of age where it approaches adult capacity
    - ❖ Example:
      - › Bumetanide – partially eliminated by tubular secretion – renal clearance increases by 3x fold over the 1st 6 months of life

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Common NICU Medications

- Antibiotics
  - Ampicillin
    - Neonate: 50 mg/kg/dose IV Q12h
    - Pediatric: 50 mg/kg/dose IV Q6H
    - ADME:
      - Excreted via renal (90%) and bile
  - Gentamicin
    - Various regimens base on PMA
    - Neonate <30 weeks;≤ 14days: 5 mg/kg/dose IV Q48H
    - Pediatric: 2.5 mg/kg/dose IV Q8H
    - ADME:
      - Hydrophilic drug = Increase Vd
      - Excreted via renal (90%)
      - Nephrotoxic

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Common NICU Medications

- Antibiotics
  - Vancomycin
    - Various dosing based on PMA
    - Neonate 29-35 weeks PMA: 10 mg/kg/dose IV Q12h
    - Pediatric: 10 mg/kg/dose IV Q6H
    - ADME:
      - Excreted via renal
      - Nephrotoxic
  - Meropenem
    - Neonate: 20 mg/kg/dose IV Q12H
    - Pediatric: 20 mg/kg/dose IV Q8H
    - ADME:
      - Excreted via renal

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Common NICU Medications

- Antibiotics
  - Ceftriaxone and Trimethoprim-Sulfamethoxazole
    - ❖ Neonate: Contraindicated in younger then 28 days who have elevated bilirubin
    - ❖ ADME:
      - › Higher affinity to albumin that can displace bilirubin and result in kernicterus

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Common NICU Medications

- Apnea of Prematuriy
  - Caffeine Base (citrate)
    - Neonate:
      - Loading dose: 10 mg/kg/dose (20 mg/kg/dose citrate) IV/PO x1 dose
      - Maintence dose: 5 mg/kg/dose (10 mg/kg/dose citrate) IV/PO Q24H
    - ADME:
      - Metabolism is reduced due to decrease activity of CYP1A2
        - Increase Half-life
        - Neonates: 96 hours
        - Pediatric: 5 hours
      - Clearance is decreased
        - Neonates: 8.9 ml/kg/hr
        - Adults: 94 ml/kg/hr

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Common NICU Medications

- Pain
  - Morphine
    - Neonate: 0.05-0.1 mg/kg/dose IV Q4-8H
    - Adult: 1 – 4 mg/kg/dose IV Q1-4H
    - ADME:
      - Metabolized via glucuronidation

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Common NICU Medications

- Neonatal Seizures
  - Phenobarbital
    - ❖ Loading dose: 15-20 mg/kg/dose IV/PO x1 dose
    - ❖ Maintenance dose: 4 mg/kg/dose IV/PO Q24H
    - ❖ Pediatric: 6-8 mg/kg/day
    - ❖ ADME:
      - › PO: absorption may be decrease due to phenobarbital being a weak acid in a higher gastric pH
      - › Hepatic metabolism: Glucuronidation and Hydroxylation
        - › Increase half life: up to 200 hours

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Common NICU Medications

- Neonatal Seizures
  - Fosphenytoin/Phenytoin
    - Loading dose: 15-20 mg/kg/dose IV x1 dose
    - Maintenance dose: 4-8 mg/kg/day IV divided Q8H
    - ADME:
      - Renally eliminated
        - Reduced renal function in neonates
        - Elevated renal clearance per kg body weight in children older >1 yr
      - Increase amount of free drug in neonates due to decrease protein binding sites and reduced albumin
        - Goals for serum level are lower in neonates
          - Neonates: 6-15 mCg/ml
          - Children/Adults: 10-20 mCg/ml
        - Highly protein bound
          - >95% protein bound

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Common NICU Medications

- Topical
  - Corticosteriods, Lidocaine, Povidone Iodine
    - ADME:
      - Increase absorption due to thinner corneum, greater cutaneous perfusion and hydration
      - Potential for toxicity due to increase total body surface area to body mass in neonates

Take Home Remarks

- Pediatric population has many changes in physiological functions as they grow, and organ system matures. These changes results in pharmacokinetic alterations
- Changes in gastric pH, decrease gastric emptying and intestinal transit may cause increase/decrease absorption of medications that is not seen in the pediatric population
- Increase in total body water composition leads to higher doses in hydrophilic drugs
- Slow drug metabolism and renal excretion requires lower mg/kg dosage and/or increase frequency to achieve therapeutic concentrations

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References

1. Allegaert K, Mian P, Van den Anker JN. Developmental Pharmacokinetics in Neonates: Maturation Changes and Beyond. Current Pharmaceuticals Design 2017;23:1-10.
2. Bartelink IH, Rademaker CMA, Schobben AF, Van den Aker JN. Guidelines on Paediatric Dosing on the Basis of Developemnetal Physiology and Pharmacokinetic Considerations. Clin Pharmacokinet 2006; 45(11):1077-1097.
3. Coggins SA, Greenberg RG. Pharmacokinetic and Pharmacodynamic Approaches to Optimize Antibiotic Use in Neonates. Clin Perinatol 2025;52:67-86.
4. Jusko WJ, Milsap RL. Pharmacokinetics in the Infant. Environ Health Perspect 1994; 102(Suppl11):107-110.
5. Kearns GL, Abdel-Rahman SM, Alendar SW, et al. Developmental Pharmacology -Drug Disposition, Action, and Therapy in Infants and Children. NEJM 2003; 349:1157-67.
6. Lim SY, Pettit RS. Pharmacokinetic Considerations in Pediatric Pharmacotherapy. Am J Health-Syst Pharm 2019;76(19):1472-1480.
7. Lexicomp Online. www.crlonline.com. July 2025.
8. Polsdorfer R. Therapeutic Drug Monitoring in Neonates. University of the Sciences in Philadelphia, Philadelphia College of Pharmacy Reports on Neonatal Pharmacotherapy. 2004.
9. Reiter PD. Neonatal Pharmacology and Pharmacokinetics. NeoReviews 2002;3:e229-e236.
10. Soldin OF, Soldin SJ. Review: Therapeutic Drug Monitoring in Pediatrics. Ther Drug Monit. 2002 Feb; 24(1):1-8.
11. Young LL, Koda-Kimble M. Applied Therapeutics, The Clinical Use of Drugs 7th ed.. Applied Therapeutics, Inc. Vancouver, WA.

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LONG LIVE CHILDHOOD

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