PRINCIPLES OF NEONATAL PHARMACOKINETICS AND DRUG THERAPY

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Terminology

- Gestational age
- Postnatal age
- Preterm
- Term
- Neonate
- SGA
- AGA
- LGA
Monitoring Parameters

- Creatinine - At birth this is the same as the mother’s creatinine.
- Heart rate is higher than adults
- Respiratory rate is higher than adults
- Lower blood pressures than adults
The Effects of Growth and Development on Drug Disposition

- Absorption
- Distribution
- Metabolism
- Elimination
## GI Absorption (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric acid secretion</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Gastric emptying time</td>
<td>Prolonged</td>
<td>Shortened</td>
<td>Shortened</td>
</tr>
<tr>
<td>Intestinal motility</td>
<td>Irregular</td>
<td>Irregular</td>
<td>Normal</td>
</tr>
<tr>
<td>Intestinal permeability</td>
<td>Immature</td>
<td>?Immature</td>
<td>Normal</td>
</tr>
<tr>
<td>Biliary function</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Microbial flora</td>
<td>Acquiring</td>
<td>Adult pattern</td>
<td>Adult pat.</td>
</tr>
</tbody>
</table>
Gastrointestinal Absorption

Two important physiological factors affect absorption
1. Gastrointestinal Motility
2. pH of the Intestinal Contents
The Effects of Growth and Development on Drug Disposition: Absorption

- Gastric acid production is decreased.
- Gastric emptying is prolonged.
- Smaller surface area of the gut.
- More erratic blood circulation to the GI tract.
- For many drugs, the only effect is a delay in absorption.
Drugs that are affected

- Absorption of carbamazepine, rifampin, phenytoin, and acetaminophen is reduced.
- Other drugs have their absorption delayed but total amount absorbed is same as adults- such as phenobarbital and digoxin.
Percutaneous Absorption

Absorption through the skin:
- Enhanced due to increased BSA to body size ratio
- Thinner stratum corneum allowing for increased absorption
- Increased skin hydration
Intramuscular Absorption

⭐ Main factors include:
- Muscle mass
- Muscle activity
- Blood flow to the site
The Effects of Growth and Development on Drug Disposition: Distribution

- Total body water content
- Fat Stores: Premature (1-2%) vs Infant (10-15%) vs 1 year old (20-25%)
- Plasma Protein Concentrations: lower amounts
Kernicterus

- The staining and subsequent damage of the brain by bile pigment (bilirubin).
- Due to decreased in serum protein binding sites there is an increase in competition and chances of kernicterus.
- Kernicterus is a result of displacing bilirubin from albumin sites.
- Drugs that have been implicated in displacing bilirubin are sulfonamides and ceftriaxone.
Plasma Protein Binding

- Binding affinity for albumin is decreased in neonates.
- This may lead to increased free drug; however, results are unpredictable since increased amount at site of action but also increased amount available for clearance.
Volume of Distribution

- The hypothetical volume of body fluid through which drug must be distributed to produce a specific serum level
- Or
- The size of a compartment necessary to account for the total amount of drug in the body if it were present throughout the body at the same conc. found in the plasma.
Major factors affecting Vd

- Lipid versus water solubility character.
- High water solubility = low Vd
  - Mainly confined to the intravascular space.
- High lipid solubility = large Vd
  - Move out of central plasma compartment and have greater tissue distribution.
Major Factors in Vd

✿ Drugs that are largely plasma protein bound (versus tissue protein bound) will have small volumes of distribution since they will remain in the plasma compartment.

✿ Most drugs are affected by both their water solubility (or lack of) and their plasma protein binding.
The Effects of Growth and Development on Drug Disposition: Metabolism

- Liver metabolism is dependent on:
  - Blood flow
  - Binding affinity
  - Rate of extraction
  - Enzyme activity
Phase I Reactions

- Phase I reactions show great variability during development.
- Phase I reactions:
  - Oxidation
  - Reduction—present and fully functional
  - Hydrolysis
  - Demethylation—reduced but present
Phase I reactions: CYP enzyme summary-Oxidative capacity

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Drugs it affects</th>
<th>adult values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>caffeine, theophylline</td>
<td>4-6 months(exceeds later)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>codeine, oxycodone</td>
<td>adult value by childhood</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>diazepam, omeprazole</td>
<td>Not studied</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>ibuprofen, phenytoin</td>
<td>Increased in neonate exceeds adults at 3yo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controversial</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>acetaminophen</td>
<td>early childhood then overexpressed then dec.</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>cbz, cisapride, methadone</td>
<td></td>
</tr>
<tr>
<td>CYP3A5&amp;7</td>
<td>similar activity as 3A4</td>
<td></td>
</tr>
</tbody>
</table>
Phase II Metabolism

- Conjugating reactions that cause more water-soluble compounds for elimination.
- Glucuronidation-limited ability in neonates and infants. (Ex: Chloramphenicol) Adult values at 6-18 months of age.
- Sulfation-well-developed in newborns. Many drugs use this pathway until glucuronidation develops. (Ex: theophylline, acetaminophen, morphine).
- Glycination- decreased but increases by 8 weeks.
- Methylation-present at birth
The Effects of Growth and Development on Drug Disposition: Elimination

- Glomerular filtration reaches adult values around 3-5 months of age. GFR is clinically mature by 30 days.
- Tubular secretion—full function is reached in the early years of life.
- Reabsorption—is reduced at birth, increase with age.
# Glomerular Filtration Rates

<table>
<thead>
<tr>
<th>Age</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-term</td>
<td>30-40 (10-20)</td>
</tr>
<tr>
<td>2 month old</td>
<td>70-80</td>
</tr>
<tr>
<td>6 month old</td>
<td>100-110</td>
</tr>
<tr>
<td>3 year old</td>
<td>100-150</td>
</tr>
<tr>
<td>Adult</td>
<td>120-150</td>
</tr>
</tbody>
</table>
Tubular Secretion and Reabsorption

- The rate of tubular function maturation occurs more slowly than glomerular maturation, reaching adult values at approximately 30-40 weeks of life.
- Factors increasing tubular reabsorption mature after tubular secretion.
Questions
Neonates are considered immunocompromised.

- Neonates have immature function of neutrophils and also decreased amounts of immunoglobulin.
- Incidence varies for sepsis- quoted to be 1-10 cases per 1000. Incidence increases in very low and low birth weight neonates.
- Meningitis occurs in approximately 10-30% of neonates with sepsis.
- Risk factors can predispose an infant to sepsis (e.g. maternal infection, fever, or prolonged rupture of membranes, or prematurity and low birth weight).
Neonatal Sepsis and Meningitis

- Clinical syndrome characterized by systemic signs of infection accompanied by bacteremia in the first days of life.

- The most common symptoms are apnea, poor feeding, temperature instability, and lethargy.

- Meningitis does not always include symptoms such as seizures, posturing, or bulging fontanelle. Meningitis should always be considered when a neonate has sepsis.
Onset Classification

- Early - 5-7 days, maternally acquired
- Late - after 5-7 days, maternally acquired or nosocomial
Pathogens

- Early onset-Group B streptococci, Escherichia coli, and other gram negative bacilli (Klebsiella pneumoniae, Enterobacter, Citrobacter, Proteus sp), Listeria monocytogenes, and Enterococcus

- Late onset-Caused by the above primary organisms or coagulase-negative staphylococcus, S. aureus, Pseudomonas, anaerobes, and Candida species. Other organisms, dependent on the nursery may also be present such as Enterobacter sp. or Serratia sp.

- S. epidermidis has become the most common pathogen in late-onset sepsis of the neonate.
Laboratory Findings

- WBC count (increased or decreased)
- ANC (increased or decreased)
- Neutropenia (WBC < 1000)
- Platelets < 100,000
- Left shift on WBC differential
- Culture positive from blood, CSF, etc.
Treatment of Sepsis and Meningitis: Early onset

- Ampicillin plus an aminoglycoside
- Ampicillin plus cefotaxime or ceftriaxone
Treatment of Sepsis and Meningitis: Late Onset

- Directed at nosocomial pathogens but need to take in consideration previous antibiotic therapy and risk factors and clinical condition (e.g. is pt. intubated, have a central line, abdominal distension present, etc.)

- Vancomycin- to cover coagulase-negative staphylococcus if central line is present. Some units will use nafcillin/oxacillin initially.

- If pseudomonas infection is suspected, piperacillin, ticarcillin or ceftazidime could be used and combined with an aminoglycoside.
## Example Antibiotic doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight &lt;1200g: 0-4 weeks (mg/kg)</th>
<th>Weight 1200-2000g: 0-7 days (mg/kg)</th>
<th>Weight 1200-2000g: &gt;7 days (mg/kg)</th>
<th>Weight &gt;2000g: 0-7 days (mg/kg)</th>
<th>Weight &gt;2000g: &gt;7 days (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (Meningitis)</td>
<td>50 q 12 hrs</td>
<td>50 q 12 hrs</td>
<td>50 q 8 hrs</td>
<td>50 q 8 hrs</td>
<td>50 q 6 hrs</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>50 q 12 hrs</td>
<td>50 q 12 hrs</td>
<td>50 q 8 hrs</td>
<td>50 q 12 hrs</td>
<td>50 q 8 hrs</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>5 q 12 hr</td>
<td>5 q 12 hrs</td>
<td>5 q 8 hrs</td>
<td>5 q 8 hrs</td>
<td>5 q 6 hrs</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>25 q 12 hrs</td>
<td>25 q 12 hrs</td>
<td>25 q 8 hrs</td>
<td>25 q 8 hrs</td>
<td>37.5 q 6 hrs</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 q 24 hrs</td>
<td>20 q 24 hrs</td>
<td>15 q 12 hrs</td>
<td>15 q 12 hrs</td>
<td>15 q 8 hrs</td>
</tr>
</tbody>
</table>
Neonatal Meningitis

- The pathogens that cause sepsis are the same that commonly cause meningitis.
- Group B strep and E. coli cause 75% of all meningitis. L. monocytogenes is the third most common pathogen for meningitis.
- May consider changing empiric antibiotics from ampicillin/gentamicin for early-onset infection to ampicillin/cefotaxime or ceftriaxone if gram-negative bacilli grows from CSF.
Duration of Therapy

- Sepsis: 7 to 10 days of therapy; if clinical response is slow and multiple areas are involved therapy may be 14-21 days.
- Meningitis: 14 days for gram-positive infections and 21 days for gram-negative infections.
- Antibiotics are normally stopped after 48-72 hrs if all cultures are negative except if clinical improvement is noticed after start of therapy or infection is highly suspected (such as pneumonia) that may not be seen in the blood cultures.
TORCH Titers

✦ Neonates who display signs of infection: irritability, thrombocytopenia, hepatosplenomegaly, fever) should be evaluated for these infections.

✦ When congenital infections are suspected diagnostic tests for each different organism should be run.

✦ A complete maternal history should also be obtained which may help in diagnosis.
TORCH Titers

- Toxoplasmosis
- Other (syphilis, gonorrhea, hepatitis B, listeria)
- Rubella
- Cytomegalovirus
- Herpes simplex virus
**Congenital Herpes**

- May be acquired in utero transplacentally or ascending infections (vaginal or cervical), perinatally via passage through the birth canal with active herpes lesions, or postnatally.
- Most commonly acquired through passage of the birth canal (90%) vs only 5% of cases each are acquired transplacentally and postnatally (through close contact).
- Primary maternal genital HSV infection at the time of delivery is a major risk factor.
**Congenital Herpes and Treatment**

- 3 patterns of HSV: disseminated with or without encephalitis, localized CNS infection, or localized SEM (skin, eyes, mouth) infection.

- Most infants present with SEM disease but a large percent (60-70%) will progress to disseminated. Mortality is >50% with disseminated vs zero for SEM.

- Acyclovir is treatment of choice. Early treatment is important.
Toxoplasmosis

- Acquired from ingesting uncooked meat or contact with infected cats.
- Newborn becomes infected by transplacental transmission. Early in gestation infection makes the disease worse.
- Therapy includes sulfadiazine and pyrimethamine. (plus folinic acid for neonate to decrease potential adverse effects of pyrimethamine)
Syphilis

- Caused by Treponema pallidum, a spirochete.
- Transmission: Acquired by direct contact with lesion of mucous membranes or skin of infected person. Vertical transmission can occur transplacentally or during delivery by contact of the newborn with genital lesions.
- Most common symptoms are hepatosplenomegaly, erythematous maculopapular rash (hands/feet mainly), bone lesions, and rhinitis.
- Treatment: Penicillin G for 10-14 days
**Hepatitis B**

- Transmitted rarely transplacentally; most newborns are infected around birth.
- 91% can become chronic carriers of HBsAG and develop hepatitis, cirrhosis, and hepatocellular carcinoma if not treated.
- Chronic carrier rate can be decreased to 0-14% with hepatitis B vaccination and hepatitis B immune globulin (HBIG).
Rubella

- Rubella incidence is not common due to vaccinations.
- No current treatment for it.
- Infection via crossing placenta results in spontaneous abortion, stillbirth, and birth defects known as congenital rubella syndrome (hearing loss, cataracts, and congenital heart defects (PDA, pulmonary artery stenosis).
Cytomegalovirus Infection

- Most common congenital infection-affects 40,000 infants each year.
- Transmission: Transplacentally at any stage during pregnancy or during delivery. Primary CMV results in higher transmission vs recurrent disease.
- Treatment: No proven effective antiviral therapy. We use IV ganciclovir to treat.
Questions
Neonatal Seizures

- Difficult to recognize
- Rarely tonic-clonic seizures, but can be clonic, tonic, myoclonic or subtle in nature
- Commonly a manifestation of a life-threatening underlying neurological process.
- Treatment is aimed at the identified etiology.
Etiology of Seizures

- Check glucose, electrolytes including sodium, calcium, and magnesium, blood gases, bilirubin, and infectious disease work-up to include CBC with platelets, blood culture, urine culture, and lumbar puncture for CSF culture. TORCH work-up may be considered.
- Consider EEG, metabolic disease work-up, CT or MRI to rule-out infarcts, hemorrhages, calcifications, or CNS malformations.
- Birth history for asphyxiation or hemorrhage.
Hypoxic Ischemic Encephalopathy (HIE)

- Most common cause of neonatal seizures.
- Often associated with hypoglycemia (Normally treat if <40mg/dL), hypocalcemia, and hyponatremia.
Treatment of Seizures

- Based on etiology: replace glucose, calcium gluconate (200mg/kg), or magnesium (25-50mg/kg).
- If electrolytes continue to be abnormal, consider adrenal insufficiency or metabolic inborn error (treat the cause).
- Antiepileptics
Antiepileptics

- Phenobarbital
- Phenytoin/Fosphenytoin
- Lorazepam
- IV pyridoxine - supplementation for life if has pyridoxine dependency
NEONATAL WITHDRAWAL SYNDROME

Due to maternal substance abuse
May induce fetal dependency
May have short and long-term effects that can affect learning, development, and behavior.
Drugs That Cause Neonatal Withdrawal

- **Opiates**-includes codeine, heroin, meperidine, morphine, methadone, etc.
- **Barbiturates**-includes phenobarbital, secobarbital, etc.
- **Others**-alcohol, benzodiazepines, propoxyphene, cocaine, methamphetamine
Withdrawal Signs and Symptoms

☆ Onset: Varies from minutes to days depending on the narcotic/medication used, time and duration of exposure, the amount of drug taken by the mother, and routes of metabolism of mother and fetus.

☆ Symptoms: Depends on drug(s) involved

☆ For narcotics-can persist 2-3 weeks after birth and in a more subacute form last for 4-6 months with a peak around 6 weeks of age.

☆ For barbiturates-can be a late onset(i.e. 1-2 weeks) and duration may be several months.
# Onset and Duration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>24-48h up to 6d</td>
<td>4 months</td>
</tr>
<tr>
<td>Methadone*</td>
<td>48-72hr to 7-14d</td>
<td>2-4 wks to 2-6 months</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1 wk of life</td>
<td>Shorter than opiates</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>1 wk of life</td>
<td>No information</td>
</tr>
<tr>
<td>Marijuana</td>
<td>3-4d of life</td>
<td>Up to 6 days</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2-14 days of life (normal 4-7 days)</td>
<td>Up to 6 months</td>
</tr>
</tbody>
</table>

*For most narcotics symptoms appear within 72 hrs.*
Withdrawal Symptoms

- CNS Hyperirritability - most common (includes hyperexcitability, high-pitched cry, fist sucking, hyperreflexia, abnormal sleep pattern, tremor, myoclonic jerks)
- Respiratory difficulties (stuffy nose, tachypnea, apnea)
- GI dysfunction (uncoordinated suck, vomiting, diarrhea, poor feeding, spitting up)
- Sneezing, yawning, hiccups, sweating, hyper or hypothermia, skin mottling
- Seizures occur infrequently; methadone has the highest incidence (10-20%)
Therapy of NWS

- **ENVIRONMENT** - A calm, quiet and dark place with decreased stimulation. This is the first line of approach. Swaddling and gentle touch. Pacifier for excessive sucking.

- **DRUGS** - Several drugs have been reportedly used.

- Indications for drugs are: seizures, diarrhea and vomiting, sleeping disorder, severe hyperactivity, irritability, tremor, or tachypnea.
Scoring Systems

- There are several scoring systems that have been designed:
  - Neonatal Abstinence Score
  - Neonatal Narcotic Withdrawal Index
  - Moro Scale Score
- It has been suggested there needs to be different scoring based on gestational age.
DRUG THERAPY

- Opiates- morphine or methadone or paregoric or tincture of opium, phenobarbital, diazepam, chlorpromazine
- Barbiturates-phenobarbital
- Alcohol-phenobarbital, diazepam, chlorpromazine
- Cocaine-Supportive care, possibly benzodiazepines
- Methamphetamines-supportive care
- Benzodiazepines-diazepam, lorazepam
Narcotic agents

- Paregoric, methadone, morphine, and tincture of opium are the most commonly mentioned narcotics used to treat withdrawal.
- They are used for narcotic withdrawal predominantly.
- They have the advantage of having constipating effects to help treat diarrhea.
Paregoric

- Paregoric is not used as commonly at this time as stated; it is the most studied narcotic for neonatal withdrawal syndrome.
- It is called “camphorated tincture of opium.”
- It contains morphine 0.4mg/ml, but also camphor, alcohol(44-46%), and other products(antispasmodics).
- 0.1ml/kg q3-4 hours. Titrate up by 0.1ml/kg/dose every 3-4 hours until symptoms controlled.
- Once symptoms controlled for 3-5 days titrate dose down gradually.
Morphine

• Varying doses; oral morphine contains less alcohol than paregoric and does not contain the unwanted additives.

• If being given in the 0.4mg/ml concentration dosing suggestions have been 0.05ml/kg every 4 hours.

• Dosing of 0.08-0.2mg q3-4hrs has been suggested. Increase by 0.02mg/dose every 3 hrs until symptoms improve (Based on paregoric dosing).

• Tapering begins 3-5 days after symptoms are under control.
Methadone

• Varying dosage ranges: 0.05mg/kg to 0.1mg/kg every 6-12 hours with 0.05mg/kg increases until symptoms are controlled is one method. Methadone may be given every 12 to 24 hours.

• Weaning is normally done in 10-20% increments every 1-3 days (or longer) depending on symptoms.
Phenobarbital

- Used for opiate or barbiturate withdrawal or alcohol or polydrug abuse.
- Does not control diarrhea associated with withdrawal.
- Decreases hyperactivity/agitation of neonate.
- Dosing is normally a loading dose of 10-20mg/kg followed by a maintenance dose of 4mg/kg/day. Dosage can be adjusted upward as necessary. A level of 20-30mcg/ml is the usual goal (and control of withdrawal).

• Tapering is usually 10-20%/day as tolerated.
Other Medications

- Diazepam is usually used for benzodiazepine withdrawal or perhaps as a prn medication for agitation/CNS hyperactivity associated with narcotic withdrawal. Doses of 0.3-0.5mg/kg q8hrs have been used.
- Chlorpromazine – to reduce CNS and gastrointestinal symptoms associated with neonatal narcotic withdrawal. Doses of 2.2-3mg/kg/day divided in 4 to 6 doses has been suggested. Dosage should be reduced 2mg/kg every 3 days after the patient is stabilized. Use is very limited.
- Clonidine is often referred to in articles; however, its use in neonates is limited. May control many narcotic withdrawal symptoms. Has been used in older children/adults.
Questions