Neonatal Pharmacology Review

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Session Summary

This presentation will provide a general overview of pharmacokinetics, pharmacodynamics, and common medications used in neonatal medicine to help prepare the participant for certification exams.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- describe the principles of pharmacology and how these differ in the fetus and neonate;
- identify drugs used in the NICU, their indications and significant side effects;
- identify drugs used in resuscitation;
- understand how drugs given to the mother may affect the fetus.

Test Questions

1. When comparing a premature infant to a older infant’s extracellular fluid volume, the volume of distribution for a water-soluble drug in a premature infant would be:
   a. equal
   b. greater
   c. less

2. A drug that is un-ionized:
   a. is unable to cross to the placenta
   b. will cross the placenta less readily
   c. will cross the placenta more readily

3. What change in a medication’s scheduling would need to happen in a premature infant with a decreased glomerular filtration rate (GFR)?
   a. decreased loading dose
   b. lengthened dosing interval
   c. shortened dosing interval

4. When using epinephrine in a resuscitation it is important to remember:
   a. that it decreases O2 consumption of heart muscle
   b. that it increases peripheral dilation
   c. that ventilation must be established
5. Dobutamine will:
   a. decrease peripheral vascular resistance
   b. does not change peripheral vascular resistance
   c. Increase peripheral vascular resistance

6. Which of the following diuretics has been associated with the most significant sensorineural hearing loss?
   a. Bumex
   b. Lasix
   c. Chlorothiazide

7. An infant is receiving Gangiclovir, the NNP should monitor the infant most closely for:
   a. anemia
   b. neutropenia
   c. renal failure

8. Which of the following antibiotics should be used to treat Chlamydia eye infection?
   a. erythromycin
   b. gentamicin
   c. streptomycin

9. Which of the following drugs is a proton pump inhibitor that blocks gastric H+ secretion into the gastric lumen?
   a. metoclopramide
   b. omeprazole
   c. rantidine

References


Session Outline

See handout on following pages.
Pharmacology Review

Lyn Vargo, PhD, RN, NNP-BC

Introduction
- The premature and full term neonates are in a rapid & continuous state of maturation.
- This influences the therapeutic and toxic effects of drug therapy.

Pharmacodynamics
- The action of drugs (or how they work).
- What the drug does to the body
- Molecular interactions between the drug & a receptor
- The receptor can be an enzyme, membrane protein or nucleic acid
- Selectivity for particular organs is possible.

Pharmacokinetics
- Pharmacokinetics: The movement of drugs.
- What happens to drugs once they enter the body.
- Pharmacokinetics include 4 parameters
  1. Absorption
  2. Distribution
  3. Metabolism
  4. Excretion

Kinetics & Dynamic Interface

Absorption
- The translocation of a drug from the site of administration into the systemic circulation
- IV drugs have rapid & complete bioavailability
- Extravascular drugs (rectal, oral, topical, inhaled & IM) must cross several membranes to reach target site
Oral Absorption in the Neonate
- Gastric acid secretion is diminished: Higher pH (6-8)
- Gastric emptying is irregular & erratic
- Gut motility is irregular (can lead to longer transit time)
- Fewer bacteria
- Greater relative small gut surface area
- Biliary function immature
- Splanchnic blood flow reduced
- Pancreatic lipase activity is decreased

Disease Processes that will Affect Oral Absorption
- Short bowel syndrome
- Protein-calorie malnutrition
- Pyloric stenosis
- Congestive heart failure
- Cholestatic Liver disease
- Extrahepatic biliary obstruction
- Thyroid disease
- Diarrheal disease
- Proximal small-bowel resection

Topical Absorption in the Neonate
- Percutaneous absorption is directly related to degree of skin hydration & relative surface area
- Ratio of surface area to body weight of neonate is higher—thus infant exposed to a relatively higher topical dose
- Percutaneous absorption is inversely related to the thickness of stratum corneum.

Intramuscular Absorption
- Influenced by site of administration, presence of pathophysiology & developmental state.
- Muscle mobility will affect (use of paralyzing agents will affect)
- Total surface area of muscle will affect
- Lipophilicity will also affect (favors rapid diffusion)

Drug Distribution
- Refers to the process of drug movement through various body compartments, tissues & cells.
- Affected by: pH, size & composition of the compartment, protein binding, membrane permeability & hemodynamic factors

Drug Distribution in Neonates
- Protein binding has a profound effect on distribution
- Unbound drug (free drug) is only one that is pharmacologically active.
- Higher % of total body water (especially preterm infant)
- Preterm infants have lower concentrations of binding proteins, presence of fetal albumin, a lower plasma pH and endogenous protein binding competitors (bilirubin & free fatty acids)
- If binding proteins decreased, there is an increased free fraction of drug
### Volume of Distribution
- Describes the relationship b/w the total amount of drug in the body & its plasma concentration.
- In premature infants and term neonates, the volume of distribution for water-soluble drugs is increased compared to adults.
- Edematous infants will have a higher volume of distribution of a drug also.
- Volume of distribution is increased, there will be a decreased peak concentration of a drug (exs: gentamicin, digoxin).

### Metabolism
- Drugs are metabolized or “biotransformed” by a variety of mechanisms.
- Original drug disappears as it is chemically changed.
- It involves the alteration of the chemical structure of the drug by an enzyme.
- This occurs most often in liver for most drugs via phase I or phase II reactions.

### Metabolism
- Before biotransformation can occur the first step is uptake of drug into hepatocyte by acceptor proteins.
- Preterm infants have lower & sometimes absent acceptor proteins.
- Concentration of these proteins increases in 1st 10 days of life.

### Metabolism
- Phase I reaction or Phase II reaction
- Phase I is often followed by Phase II
- Phase I: preparatory & includes oxidation, reduction, hydrolysis & hydroxylation—Most of these are present at birth (even in preterms) but are reduced.
- Phase II: referred to as conjugation & includes: glucuronidation, sulfation, acetylation & methylation.

### Metabolism
- Phase I reactions are mostly cyps (cytochrome enzyme systems)
- Cytochrome P450 family are most commonly involved in the metabolism of fat soluble drugs (it is reduced in the neonate)
- Phase II reactions show limited activity in fetal life & mature at different rates postnatally.

### Elimination
- Excretion of a drug. Most done by kidneys
- Dependent on the renal system, glomerular filtration rate (GFR) & tubular function
- GFR is gestational age related & is reduced with increasing prematurity
- At 40 weeks GFR is 2.0-4ml /min, which increases rapidly to 50% of adult levels by 3months.
- This leads to inefficient renal excretion & a prolonged elimination half-life in the neonate.
- If GFR decreased than dosing intervals will need to be lengthened.
Important Concepts Related to Elimination

- **First order kinetics**—The rate of elimination is proportionate to plasma concentration
- The elimination of drugs that follow first order kinetics can be characterized by a proportionality constant clearance.
- **Clearance** is defined as:
  \[ Cl = \text{rate of elimination/plasma concentration} \]

Half-life—time needed for the blood concentration of a drug with first order clearance to fall by 50% during the elimination phase.

Steady state—the point of equilibrium where drug in equals amount of drug excreted.

Half-life is important because it determines both the amount of time to reach steady state (3-5 half lives) & the appropriate drug dosing interval.

When dosing neonates, the prolonged half life of many drugs warrants longer intervals to prevent overdosage & toxic effects.

### Therapeutic Drug Monitoring

- Often used when there is a narrow therapeutic range, severe toxic effects or other pathology.
- Exs: gentamicin, vancomycin, amikacin
- **Peak level**—drawn after dose given (will depend on drug & infusion rate). If PEAK HIGH, the dose should be DECREASED.
- **Trough level**—drawn prior to dose. Dependent on interval of drug. If TROUGH HIGH, the dosing interval should be EXTENDED.

### Pregnancy & Pharmacology

- There are significant changes in ADME in pregnancy.
- Most drugs cross placenta by simple passive diffusion & depends on concentration gradients.
- Factors that increase transfer for type of drug include lipid solubility, low molecular weight (less than 600 daltons for nonsoluble & less than 100 for polar substances), un-ionized & with low protein binding.
- Water soluble (polar), have a high MW (>600 daltons), ionized & highly bound to protein do not cross as easily.
- Insulin & heparin do not cross placenta

- Several forms of CYP450 system are found in placenta (phase I reactions).
- Phase II reactions are also seen in placenta throughout pregnancy & may increase with nicotine or alcohol abuse.

- Liver of fetus is fairly well developed.
- Mirrors the placenta in its capacity to metabolize.
- In the fetus, the metabolic activity of CYP-mediated reactions is less than in the adult.
- Any blood going through placenta will enter fetus & either enter liver for possible metabolism or go through ductus venosus & may enter the fetal circulation unmetabolized & distributed to fetal receptors.
Known Teratogens

- Lithium—malformation Ex: Ebstein anomaly
- Salicylates—problems with platelets & possible closure of PDA
- Androgens
- Progestins—(depending on time given)
- Warfarin
- Anti-thyroid medications (goiter, etc.)
- Thiazides—thrombocytopenia, altered carbo metabolism, ^ bili
- Valproic acid
- Alcohol

Antenatal Tocolysis

- Magnesium Sulfate—very common & safe. Also good for pre-eclampsia.
- Similar efficacy as terbutaline but less side effects.
- Given by IV & readily crosses placenta
- No heart rate variability noted in fetus
- Neonatal effects: apnea, hypotension, respiratory depression, hypotonia & decreased peristalsis

Antenatal Tocolysis

- Beta-sympathomimetic agents: Ritodine (IV & oral) & terbutaline (most commonly used)(subq, oral or IV)
- Used as tocolytic & for tetanic cx
- Fetal effects: tachycardia, Neonatal hypoglycemia

Antenatal Tocolysis

- Indomethacin (orally or rectally)
- May be safe but should be used for less than 48 hours & less than 30-32 weeks gestation. Longer term usage is associated with fetal effects.
- Fetal effects: oligohydraminos, constriction of ductus arteriosus, decreased urine output.

Use of Prenatal Corticosteroids

- NIH consensus statement 1994: antenatal administration of betamethasone or desamethasone significantly reduce the incidence & severity of RDS, IVH & potentially NEC.
- All fetuses b/w 24-34 weeks gestation at risk for preterm delivery & that are eligible for tocolytic therapy should receive antenatal steroids.
- Of repeat doses addressed in 2000—repeat dosing should not be administered outside of randomized trial.

Maternal Anesthesia & Analgesia

- Nerve Blocks
  - Paracervical: blocks pain transmission via the visceral afferent fibers near dilating cervix. Uses local anesthetic. Less commonly used now. Low complication rate
  - Pudendal: reserved for delivery phase of 2nd stage. Often used with forceps. Uses local anesthetic. Some seizures have been seen.
Maternal Sedatives

- Use has diminished. Extremely anxious Moms
- Most common benzodiazepines (diazepam & midazolam). Midazolam does not cross to fetus well. Diazepam can cause respiratory depression, hypothermia & hypotonia in neonate.
- Barbituates: most common seconal (sleeping aid). Long safety record in fetus. Metabolized quickly. Barbituates have a known antianalgesic effect.

Maternal Opioids

- Compound that acts on same receptors as morphine & produces same effect.
- Includes morphine, fentanyl, demerol & stadol
- Alter the perception of pain & one's response.
- Use of these in labor generally occur early.
- Fetal effects: can cause decreased beat-to-beat variability, respiratory depression. Decreased oxygenation.
- Use of naloxone (narcan): commonly used to reduce effects of opioid. Should not be given to Mom with narcotic addiction!

Maternal Substance Abuse

- 3 stage effect of antenatal street drug use:
  1. Affects fetus in utero: teratogenic effect
  2. Affects neonate after delivery with withdrawal from drug exposure

Common Street Drugs

- Tobacco
- Heroin/Methadone
- Marijuana
- Opioids
- Cocaine
- Amphetamines
- Crack/Ecstasy/Crystal meth
- Benzodiazepine

Fetal Alcohol Syndrome (FAS)

- FAS leading cause of mental retardation and neuro deficit in the western world.
- Growth restriction
- Specific mid facial features.
- Adverse brain effects yielding mental retardation & structural defects.

Heroin/Methadone

- Heroin is a CNS depressant that is 6x as potent as morphine. Illegal. Highly addictive.
- Not generally thought of teratogenic.
- Infants exposed to weigh significantly less, may have passive addiction. May have fetal distress
- May treat Mom with methadone instead.
Cocaine

- A CNS stimulant that induces vasoconstriction to vascular beds.
- CRACK has become popular—purer form that is a cocaine alkaloid. It is highly addictive.
- Pregnant women are slower to metabolize cocaine.
- Felt to be most dangerous of all illicit drugs.
- Risks to fetus include, spontaneous abortion, placental abruption, placental vasoconstriction which can inhibit O2 transfer to fetus. Preterm labor, LBW, SGA, NEC. Teratogen (limb defects, microcephaly, GI/GU abnormalities, facial defects, neural tube defects)

Neonatal Abstinence Syndrome

- Seen in babies of mother’s who abused antenatal drugs.
- Withdrawal can occur up to DOL 6.
- Includes CNS & GI symptoms. Hyperactivity, irritability, tremors, high pitched cry, hypertonicity, and convulsions. Many infants are IUGR
- Seems to last longer with methadone withdrawl.
- SIDS more common (especially with cocaine)
- Developmental issues with cognitive and language delays. Behavioral problems etc. Lower IQ. Decreased motor skills.

Treatment of Neonatal Abstinence

- Drugs that can cause NAS are opioids alcohol, barbiturates, caffeine, diazepam SSRIs & cocaine (most common with opioids)
- Nutritive, environmental & pharmacologic treatment.
- Use optimum nutrition, hyper caloric feeds. Swaddling, quiet environment & decreased stimuli.

Pharmacologic Treatment of NAS

- Morphine—most commonly used
- Methadone—Well absorbed from GI tract (better than morphine) but it has a long half life & there are problems with its use due to this.
- Tincture of opium—contains several narcotic alkaloids including codeine & morphine.
- Phenobarbitol—sedative effect. Often used with opiate.
- Diazepam—prolonged metabolism & thus elimination
- Paregoric—No longer used due to high ethanol & other issues.

Drugs Used in Resuscitation

- Know when to give medications per NRP
- UVC is the quickest & preferred route to give medications. ET tube, Intraosseous

Epinephrine

- Stimulant that increases strength & rate of cardiac contractions.
- Most Importantly: Causes peripheral vasoconstriction which increases blood flow to brain & coronary arteries. Also v diastolic BP
- Use if HR remains <60 despite adequate ventilation.
- Will increase workload & O2 consumption of heart muscle which w/o O2 may cause myocardial damage
- Dose: 1:10,000 solution: IV 0.1-0.3mg/kg, ET 0.5-1mg/kg. Rapidly. Can repeat every 3-5 minutes.
**Volume Expanders**
- Use with continued bradycardia after epi & suspicion of blood loss
- Volume expanders: For acute bleeding & hypovolemia as seen with abruption, placenta previa, vaso previa.
- 0.9% NS or Ringer's lactate (not albumin)
- Non cross matched O Rh-negative blood
- 10ml/kg x 1-2 IV over 5-10 minutes

**Naloxone**
- Narcotic antagonist that is given to babies with depressed resp. effort from maternal narcotics
- NOT necessary during acute phases of resuscitation. However, improvement in respiratory effort after giving will confirm that problems were related to maternal narcotics.
- Don't give if Mom is suspected of using narcotics or is on methadone. May induce withdrawal/seizures.
- Dose: 1mg/ml solution. 0.1mg/kg IV preferred. IM acceptable but expect delayed onset of action.

**Sodium Bicarbonate**
- Use is controversial
- May improve metabolic acidosis BUT may be harmful if given too early in resuscitation.
- May increase pH but worsen intracellular acidosis.
- Must make sure adequately ventilating baby as when mixes with acid, CO2 is formed.
- Dose if given: 2meq/kg 4.2% solution (0.5meq/ml).
  Give IV in large vein with good blood return (hypertonic & irritate to blood vessels). No faster than 1meq/kg/minute. Give slowly to preterms.

**Respiratory Drugs**
- Surfactant
- Nitric Oxide
- Bronchodilators
- Sildenafil
- Vitamin A

**Surfactant**
- Use for treatment of RDS or surfactant deficiency.
- **REDUCES alveolar surface tension!!**
- Helps prevent collapsing of alveoli & keeps interstitial fluid from entering alveoli.
- Can normalize alveolar size. Decreases air leaks
- Decreases amount of pressure required to open alveoli
- Increase in maximal volume at maximal pressure.
- Stabilizes lung (especially on deflation) & promotes gas exchange. Improves oxygenation.

**Nitric Oxide (NO)**
- Used for treatment of PPHN.
- Selectively decreases pulmonary vascular resistance & relaxes smooth muscle.
- Dose: 5-20 ppm of continuous inhaled gas.
- Will not cause systemic hypotension.
- Side effect--Methemoglobinemia
**Vitamin A**
- Vitamin A is essential for growth & differentiation of epithelial tissues.
- Premature infants have low levels of Vit A at birth & infants with lung disease have even lower levels.
- Supplement with 500 IU 3X/week for 4 weeks. Given IM
- Reduces risk of death or O2 supplementation at 1 month by 7%.

**Bronchodilator**
- Albuterol: selective beta₂ adrenergic agonist that relaxes smooth muscle & allows bronchodilation
- Use meter dosed inhaler
- Improves compliance & resistance
- Can have tachycardia

**Sildenafil**
- Specific PD5 inhibitor—lung is rich in this. It promotes pulmonary vasodilation.
- Use for treatment of PPHN refractory to NO & for infants with BPD
- Use in neonates has limited data.

**Cardiovascular Drugs**
- Dopamine: sympathomimetic, adrenergic agonist. Will increase BP by increasing systemic vascular resistance. Selective renal vasodilation at low doses (2 to 5 mcg/kg/min) with increase in urine output
- Dose: 2 to 20 mcg/kg/min (if higher consider adjunctive drugs) by continuous IV infusion.
- Adverse effects: vasoconstriction, tachycardia. Tissue sloughing with infiltration
- Don’t use UAC to infuse

**Cardiovascular Agents**
- Digoxin (IV/PO): digitalis glycoside with + inotropic & negative chronotropic actions. Used to treat CHF & arrhythmias. Dose depends on age & route
- Dose: Loading dose usually used with treating acute CHF & arrhythmias. Dose depends on age & route
- Adverse Effects: monitor heart rate & rhythm. Periodic EKGs indicated. Toxic effects include PR interval prolongation, sinus bradycardia, SA block, atrial & nodal ectopic beats & ventricular arrhythmias
Adenosine

Use: Treat SVT by depressing sinus node automaticity & A-V node conduction. May be useful in establishing cause of SVT.

Dose: 0.05-0.1mg/kg rapid IV push. If not effective repeat in 1-2 minutes.

Adverse Effects: don’t use with 2nd & 3rd degree A-V block. Transient or prolonged asystole.

Treatment of PDA

Indocin/Indomethacin: closure of PDA by inhibition of prostaglandin synthesis.

Side effects: GI perforation, prolonged bleeding. Platelet dysfunction. Oliguria

Ibuprofen: NSAID that inhibits prostaglandin synthesis & closes ductus. Efficacy comparable to indocin except LESS oliguria.

Side effects: GI irritation, use with care if infection present (may mask signs). May inhibit platelet aggregation.

Treatment of PDA

Alprostadil

Prostin (Prostaglandin E): keeps ductus open in ductal dependent lesions.

GI drugs--GERD

Three types of treatment:

1. Histamine-2 receptor antagonist: Suppression of gastric acid with histamine-2 receptors. These drugs decrease basal & meal-induced acid production by gastric parietal cells & thus increase pH. They decrease the acidity of esophageal reflux. Believed to decrease mucosal damage & discomfort.

Ex: Ranitidine (Zantac) Concerns with this treatment are that gastric acidity may play a role in host immune defense. ? risk of NEC, late onset sepsis, Decreasing acid production may decrease Ca absorption

2. Proton pump inhibitors (PPIs). Powerful blockers of gastric acid secretion. Irreversibly reverse the gastric H+/K+ adenosine triphosphatase responsible for secreting H+ into gastric lumen.

Exs: Lansoprazole (Prevacid) & omeprazole (Prilosec): Most commonly prescribed PPIs for infants. Presently off label use in infants less than 1 year. Many of the same concerns as H2 blockers. In one study, nonsignificant increased incidence of lower respiratory infections. Also concern for bone fractures. ? Vitamin B12 absorption
GI Drugs-GERD

3. Prokinetics. Drugs that promote gastrointestinal motility. Believed to decrease GER by increasing gastric emptying thus, limiting amount of liquid available to reflux. May also improve esophageal motility & lower esophageal sphincter tone
- Exs: Metoclopramide (Reglan). is a dopamine D2 receptor subtype. No evidence that it improves GERD. Crosses blood brain barrier & may see neurologic effects. ? Dyskinesia
- Erythromycin promotes GI migrating motor complexes. Uses doses less than w/antibiotics. May increase concentration of other drugs. Arrhythmias.

Antibiotics Used to Treat Bacterial Infection

Early Onset Treatment: In US antibiotics should cover GBS, E. Coli, & other gram-negative enteric bacilli & Listeria.
- Ampicillin with aminoglycoside commonly used (listeria & GBS are sensitive to ampicillin) whereas the susceptibility of E. coli to ampicillin less reliable.
- Gentamicin acts synergistically with ampicillin against GBS & Listeria.
- Gentamicin often used with tobramycin & amikacin reserved for treatment of multi drug resistant bacteria
- If meningitis, consider replacement of aminoglycoside with cefotaxime for better CNS penetration.

Late Onset Treatment: In community: treat with same coverage as those discussed in previous slide & also cover for S. pneumoniae & Neisseria. Ampicillin & third generation cephalosporin (cefotaxime) commonly used.
- Late onset hospital based: consider CONS, enterococci, gram-negative enteric & fungi.
- Virtually all staph are resistant to ampicillin & penicillin.
- Vancomycin & gentamicin are then commonly used initially.

Antibiotics Used to Treat Bacterial Infection

Amikacin: aerobic gram-negative infections (limit use to gent resistant organisms)
- Cefotaxime: sepsis & meningitis caused by susceptible gram-negative organisms (good CSF penetration)
- Ceftriaxone: sepsis, meningitis, soft tissue & bone/joint infections (can’t use against staph, Listeria, enterococci or pseudomonas. Used for gonococcal infections. Watch with hyperbilirubinemia. Use with calcium containing solutions contraindicated.

Antibiotics Used to Treat Bacterial Infection

Clindamycin: susceptible anaerobic organisms.
- Erythromycin: **Chlamydia, Pertussis species, minor staph or streptococcal skin infections. No significant toxicity (can treat ureaplasma also)
- Gentamicin: not effective alone but synergy with ampicillin against GBS, enterococci & Listeria. Possible ototoxic& nephro toxic & neuromuscular blockade. Activity low in CSF. Must follow levels
**Antibiotics Used to Treat Bacterial Infection**
- Nafcillin/oxacillin: treatment of penicillin resistant staph aureus. Not a first line agent to streptococci (but active against).
- Streptomycin: Mycobacterium tuberculosis, Can cause vestibular & auditory damage. Nephrotoxic. Must be given IM
- Tobramycin: broad coverage of gram – bacteria. Low CSF activity. Possible ototoxic & nephrotoxic. Monitor levels

**Antibiotics Used to Treat Bacterial Infection**
- Vancomycin: effective for CONS, meth resistant Staph aureus, & most gram positive aerobic organisms. Possible ototoxic, earlier preparations nephrotoxic. Monitor levels.
- Chloramphenicol: wide spectrum, bactericidal to H influenzae & Neisseria meningitidis. Treatment of infections resistant to all other antibiotics (salmonella) "Gray Baby" syndrome—vasomotor collapse related to immature hepatic fx. Must be monitored closely!! Levels higher than 50mcg/ml dangerous.

**Neonatal Eye Infections**
- Erythromycin eye ointment will prevent neonatal gonococcal ophthalmia. If frank infection. Treat with IV ceftriaxone.
- Infants born to mothers with untreated gonorrhea should be treated with single injection of ceftriaxone.
- Chlamydia is the leading cause of conjunctivitis in neonate. Also prevented with erythromycin (also responds to tetracycline, or silver nitrate), but if infection occurs should treat with oral erythromycin.

**Antifungal Medications**
- Amphotericin B: gold standard treatment of systemic fungal infection. Binds to fungal cell wall & causes damage.
- Half life 15 days. Highly protein bound. Lipophilic
- Hypokalemia (<3) & transient increase in serum creat occurs in ~16% of pts. Renal blood flow & GFR may be decreased by 20-60%.
- Must monitor CBC, electrolytes, UO, BUN & creat at least every other day.
- Also have 3 different lipid-associated formulations that offer better delivery, reduced toxicity & increased daily dose of parent drug.

**Antifungal Medications**
- 5-Florocystosine (5FC): antimycotic activity thought to enhance the antifungal activity of amphotericin B, especially in sites where it is thought that amphotericin penetration is suboptimal such as CSF, heart valves & vitreal body. Should not be used alone as resistance may develop.
- Assess renal fx & GI status closely. Periodic AST & ALT. Extreme caution with impaired renal fx. Amphotericin B may increase toxicity by decreasing renal fx. Fatal bone marrow suppression may occur. Use is discouraged in premature infants.
- Oral only available.
**Antiviral Medications**
- Acyclovir: Used for Herpes Simplex virus. May also be used for treatment of varicella zoster infection.
  - 20mg/kg/8 hours IV for 14 days (for CNS extended to 21 days).
  - Care should be taken when infiltrates can cause nephrotoxicity in dehydrated or renal compromised infants.
  - Can be neurotoxic in renal compromised infants.

- Gangiclovir: used to treat CMV.
  - Compared with no treatment prevented hearing deterioration at 2 years.
  - Myelosuppression is most common adverse effect (~2/3 of treated infants have neutropenia).
  - Thrombocytopenia in 20%.

- Ribaviran: used to treat RSV.
  - Approved for lower respiratory tract infections caused by RSV (but indications in spontaneously breathing & ventilated infants controversial).

**HIV Treatment in Neonates**
- HAART therapy.
  - In pregnant women therapeutic strategies to prevent mother-baby transmission include guidelines for antiretroviral drugs intragestationally & postgestationally. (Has decreased transmission to 1.5% or less in mothers who don't breast feed).
  - Use of zidovudine IV (AZT) in Mom til cord clamped & 2mg/kg/dose orally or 1.5mg/kg IV q 6 hours for 6 weeks in infant. Dosing should be started by 8-12 hours of life.
  - Anemia/neutropenia may be seen in treated infant.

**Diuretics**
- Lasix (furosmide) (po/IV/drip): loop diuretic (inhibits Na reabsorption in the ascending limb of loop of Henle).
  - See losses of Na+, K+ & Cl-.
  - Urinary Ca+ & Mg+ excretion increased.
  - Has been associated with sensorineural hearing loss in preterm infants. Aminoglycoside + lasix risk.

- Bumex (Bumetanide) po/IV: (loop diuretic) similar mechanism as lasix.
  - Urine Na losses are lower than with lasix, but urine Ca+ losses are higher.
  - Less ototoxic than lasix.

  - May have increase in K+ plasma levels.

- Chlorothiazide (Diuril)(po/IV)/Hydrochlorothiazide (po): thiazide diuretic that inhibits Na reabsorption in the distal tubule causing excretion of Na, Cl-, K+, bicarbonate, Mg+, phosphate, & water. Less Ca+ losses in urine.
  - Use in mild to moderate hypertension.
**Drugs used for Apnea**

- Theophylline/caffeine: methylxanthines cause respiratory stimulation, improvement in respiratory muscle contraction, altered sleep state, metabolic rate, etc. increase minute ventilation, decrease PaCO2 & increase resp. drive.
- Exert similar pharmacodynamics but caffeine has less peripheral side effects, slower drug clearance than theophylline. Has a stable plasma level at steady state, prolonged plasma half-life (thus only once a day dosing), does not require drug monitoring.
- May cause GE reflux, tachycardia, arrhythmia,

**Seizure Medications**

- Phenobarbitol: used as an anticonvulsant to control seizures. Limits seizures by increasing inhibitory neurotransmission. Also used for withdrawal & sedation. Used for cholestasis.
- Must have drug levels checked (trough level).
- Toxic effects include: sedation (>40mcg/ml) & respiratory depression (>60mcg/ml), irritation to veins.

**Seizure Medications**

- Phenytoin: Used to treat seizures refractory to phenobarbital. Works by blocking voltage sensitive Na+ channels, thus inhibiting repetitive neuronal firing.
- It is highly unstable in any IV solution. Don't use IM. Only compatible with NS.
- Don't give any faster than 0.5mg/kg/min to avoid cardiac toxicity, bradyarrhythmias & hypotension.
- Drug monitoring recommended.
- More expensive though.

**Seizure Medications**

- Fosphenytoin: It is a water soluble prodrug of phenytoin. It has no known intrinsic pharmacologic property before conversion to phenytoin. It is metabolically converted to phenytoin.
- Benefits over phenytoin include aqueous solution without propylene glycol, more neutral pH, compatible with D5W or NS and may be administered IM.
- Cardiac toxicity, during IV infusion, local reactions less than with phenytoin. May be given 3x faster than phenytoin.

**Seizure Medications**

- Keppra/Levetiracetam (LEV): Recently has been used as an alternative to phenobarbital for management of seizures in neonates.
- Adverse effects include somnolence, fatigue, ataxia, headache & behavioral changes.
- Pyridoxine: pyridoxine deficiency or Vitamin B6 deficiency is a rare cause of neonatal seizures. An infant with seizures that are nonresponsive to conventional therapy should receive an IV injection of pyridoxine to look for termination of seizures w/ minutes to an hour if this is the cause of the seizures.

**Pain Medication**

- Fentanyl (IV or drip): Used for analgesia, sedation & anesthesia. It is a synthetic opioid narcotic analgesic.
- 50-100x as potent as morphine.
- May see chest wall rigidity unless given over 3-5 minutes, respiratory depression, urinary retention. May have withdrawal w/ > 5 days use.
- Have Narcan available.
- Less hypotension, Less GI motility issues.
- Less histamine release—more suitable for BPD due to less airway narrowing.
### Pain Medication
- **Morphine (IV/IM/SQ):** Used for analgesia, sedation, & NAS. Stimulates opioid receptors in CNS.
- Can have respiratory depression, hypotension, bradycardia & ileus.
- Have narcan available.
- Tylenol (oral or rectal): Used for mild to moderate pain reduction & fever reduction.
- Liver toxicity can occur with excessive doses.

### Muscle Relaxants
- **Pavulon (Pancuronium)/Rocuronium/Vercuronium (iv or drip):** Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Can improve oxygenation, reduce fluctuations in cerebral blood flow & reduce barotrauma.
- Sensation remains intact. Analgesia should also be used.
- Hypoxemia may occur due to inadequate ventilation. Tachycardia & blood pressure changes. Increased salivation.
- Can be reversed by neostigmine & atropine.

### Corticosteroids
- **Dexamethasone:** adrenal corticosteroid. Anti-inflammatory glucocorticoid used to facilitate extubation & improve lung fx in infants at risk for BPD.
- Many risks involved with use & 2002 AAP strongly discourages routine use of this. May have increased risk of cerebral palsy.
- Do not give concurrently with indomethacin.

### Corticosteroids
- **Hydrocortisone:** is the main adrenal corticosteroid with primarily glucocorticoid effects. Used for treatment of cortisol deficiency, treatment of vasopressor resistant hypotension.
- May see water & Na+ retention, Hypertension, Hyperglycemia.
- Do not use concurrently with indomethacin as there is an increased risk of GI perforation.
- Not associated with increased risk of CP.

### TPN Cholestasis
- **Phenobarbitol:** stimulates bile flow…use is debatable.
- **Actigall (ursodial):** facilitates bile excretion. Can have vomiting, diarrhea & rash.

### Drugs & Lactation
- Most drugs enter breast milk by passive diffusion. Depends on molecular weight, degree of ionization, protein binding, lipid solubility & specific uptake.
- <200 daltons appear freely. Insulin & heparin don’t enter BM.
- The drug must act locally in gut or be absorbed to effect. Rule: if drug not orally bioavailable, the infant will not absorb (ex: vancomycin).
- Use single agents if possible, when multiple drugs--use one that passes least, avoid nursing at peak plasma times, s/s should be correlated with Mom’s drugs.
Remember the Principle of

Primum non nocere
First, do no harm
When treating infants with drugs, avoid exposure to meds that have documented risk & little evidence for efficacy