



Caffeine Addiction Starts in the NICU- A Deeper Look at Pediatric Medication Use

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Objectives

- Identify pediatric-specific dosage forms
- Recognize the rationale for use of selected medications in the pediatric population
- Apply knowledge to promote safe use of medications in the pediatric population



Disclosure

I have no relevant financial relationships to disclose related to this presentation.



Questions from my staff...

*Why does a baby
need caffeine?*

*Why would a baby
need sildenafil?*

Why is that pediatric pharmacist
so particular about the dosage
forms for her patients?



Case

Due to a medication shortage, the heparin flushes used in the NICU are unavailable. You do which of the following?

- A. Stock the NICU with an alternative concentration that is used in the adult units
- B. Purchase an alternative product with benzyl alcohol
- C. Stare blankly at your computer because you don't know what is special about NICU heparin flushes so you don't know how to look for the best alternative



Pediatric Dosage Forms

- Preservatives
- Excipients
- Novel concentrations



Preservatives in Pediatrics

- Benzyl alcohol is frequently used as a preservative
- Impaired clearance in neonates leads to accumulation of toxic metabolites
- Toxicity
 - Metabolic acidosis
- Preservative-free medications are recommended for the pediatric population

Valeur KS. *Pharmaceutical Medicine* (2018) 32:251-258.



Excipients

- Inert additives to pharmaceutical products can produce significant adverse effects
- Propylene glycol is a vehicle for some medications
- In the neonatal population repeated dosing can lead to accumulation
- Toxicity
 - Hyperosmolarity
 - Metabolic acidosis

Valeur KS. *Pharmaceutical Medicine* (2018) 32:251-258.



Novel Concentrations

- Weight-based dosing leads to small doses which may be difficult to measure
- Pediatric dilutions allow for more precise measurement
- Multiple concentrations may introduce opportunity for filling errors



Institute for Safe Medication Practices (2006). Accessed online: www.ismp.org/resources/infant-heparin-flush-overdose



Case

Due to a medication shortage, the heparin flushes used in the NICU are unavailable. You do which of the following?

- Stock the NICU with an alternative concentration that is used in the adult units
- Purchase an alternative product with benzyl alcohol
- Discuss the shortage with the pediatric pharmacist to identify the best alternative product



Take-Home Points

- Use preservative-free dosage forms for pediatric patients
- Avoid propylene glycol in pediatric medications (if possible)
- Double-check the concentration and volume of medications used in pediatric patients
- Consult with a pharmacist when ordering alternative products for pediatric patients during medication shortages



Case

As the inventory specialist you are adjusting the par levels for medications and notice alprostadil has not been used in over 6 months. You do which of the following?

- To decrease your inventory on-hand, return all product and no longer keep any in-stock
- Keep your current stock, but not re-order once the current supply expires
- Scratch your head because you have never even heard of alprostadil and have no idea whether it should be on your shelves

Novel Pediatric Medications



- Caffeine
- Cefotaxime
- Alprostadil
- Ibuprofen lysine
- Sildenafil

Caffeine

- Infants born prematurely have an underdeveloped respiratory drive
- At risk for apnea of prematurity
- Methylxanthines increase central respiratory drive
 - Caffeine
 - Aminophylline
 - Theophylline



Dinh KL. Apnea of Prematurity. In: Benavides S, Nahata M, eds. Pediatric Pharmacotherapy, 2013.

Cefotaxime

- Neonates are at risk of developing hyperbilirubinemia
 - Limited albumin binding sites can lead to elevated free concentrations
 - Excessive elevation in bilirubin can lead to kernicterus
- Third generation cephalosporins are used for gram-negative coverage in sepsis evaluations
 - Ceftriaxone
 - Cefotaxime
- As opposed to ceftriaxone, cefotaxime does NOT displace bilirubin from albumin

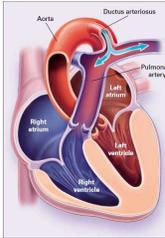


Donnelly PC. *Pediatr Drugs* (2017) 19:21-34.

Alprostadil-Background

- The ductus arteriosus is an element of fetal circulation
- Bypasses pulmonary circulation in utero
- Closure after birth occurs in part due to a decrease in circulating prostaglandins
 - Prevents mixing of de-oxygenated and oxygenated blood



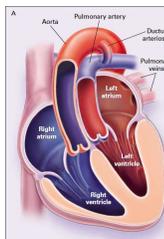


Brickner ME. *NEJM* (2000) 342(4):256-263.



Alprostadil

- Cyanotic congenital heart diseases cause a decrease in systemic circulation of oxygenated blood
 - Transposition of the great arteries
- Mixing of de-oxygenated and oxygenated blood supply through ductus arteriosus are essential to sustain life
- Prostaglandins vasodilate the ductus arteriosus to maintain patency
 - Alprostadil

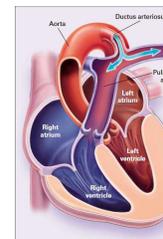


Brickner ME. *NEJM* (2000) 342(5):334-342.



Ibuprofen Lysine

- Persistent patency of ductus arteriosus can lead to pulmonary overcirculation
 - Pulmonary hypertension
- Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease production of prostaglandins promoting ductus closure
 - Ibuprofen lysine
 - Indomethacin



Brickner ME. *NEJM* (2000) 342(4):256-263.



Sildenafil

- Pulmonary hypertension occurs when pulmonary pressures exceed systemic pressures
 - Leads to hypoxia
- Cyclic guanosine monophosphate (cGMP) contributes to pulmonary vasodilation
- Phosphodiesterase inhibitors decrease the breakdown of cGMP
 - Sildenafil

Lakshminrusimha S. *Semin Perinatol* (2016) 40(3):160-73.



Case

As the inventory specialist you are adjusting the par levels for medications and notice alprostadil has not been used in over 6 months. You do which of the following?

- To decrease your inventory on-hand, return all product and no longer keep any in-stock
- Keep your current stock, but not re-order once the current supply expires
- Consult with a pharmacist regarding the appropriate par level to keep on-hand for emergencies



Take-Home Points

- Some medications are used in pediatrics for very different indications than those in adult patients
- Drug class substitutions may not always be appropriate for pediatric patients
- Consult with a pharmacist prior to returning infrequently used products for pediatric patients



Case

The price of cefotaxime tripled due to a manufacturer shortage. When you call your distributor they inform you that the price of a similar medication, ceftriaxone, is much more affordable. You do which of the following?

- Defer purchasing cefotaxime and increase your stock of ceftriaxone
- To stockpile supply, immediately order triple the amount of cefotaxime than your usual order without consulting with a pharmacist
- Decide you need to find a better yoga class to find your zen since these shortages are driving you nuts



Medications Avoided in Pediatrics

- Ceftriaxone
- Sulfamethoxazole/Trimethoprim
- Tetracyclines
- Fluoroquinolones



Ceftriaxone

- Displaces bilirubin from albumin binding sites
 - Biliary sludging
 - Kernicterus
- Interaction with calcium-containing products in neonates
 - Precipitation in lungs and kidneys
- Avoid in pediatric patients under 1 month of age

Bradley JS. *Pediatrics* (2009) 123(4):e609-13.
Donnelly PC. *Pediatr Drugs* (2017) 19:21-34.



Sulfamethoxazole/Trimethoprim

- Displaces bilirubin from albumin binding sites
 - Biliary sludging
 - Kernicterus
- Avoid in pediatric patients less than 2 months of age

Wadsworth SJ. *Antimicrob Agents Chemother* (1988) 32:1571-1575.



Tetracyclines

- Permanent dental staining and alteration of bone growth
- Avoid in pediatric patients under 8 years of age unless benefits outweigh risks

MacDougall C. Protein Synthesis Inhibitors and Miscellaneous Antibacterial Agents. In: Brunton L, ed. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 13e. 2018.



Fluoroquinolones

- Cartilage malformations noted in beagle puppies
- Increased rate of arthropathy in pediatric patients receiving fluoroquinolones
- Avoid in pediatric patients unless benefits outweigh risks
 - Cystic fibrosis
 - Multidrug resistant pathogens

Beauduy CE. Sulfonamides, Trimethoprim, & Quinolones. In: Katzung BG, ed. *Basic & Clinical Pharmacology*, 14e. 2018.



Case

The price of cefotaxime tripled due to a manufacturer shortage. When you call your distributor they inform you that the price of a similar medication, ceftriaxone, is much more affordable. You do which of the following?

- Defer purchasing cefotaxime and increase your stock of ceftriaxone
- To stockpile supply, immediately order triple the amount of cefotaxime than your usual order without consulting with a pharmacist
- Consult with a pediatric pharmacist about the best management strategy



Take-Home Points

- Some commonly used medications can be harmful in the pediatric population
- Consult with a pharmacist prior to ordering alternative products for pediatric patients due to drug shortages



Case

You are training a new technician in nonsterile compounding. While checking a dose of clonidine prepared by your orientee, you notice 1 mL was drawn up into the syringe as opposed to the ordered dose of 0.1 mL. You do which of the following?

- Ridicule the new tech in front of all the pharmacy staff to assure this mistake never happens again
- Leave the dose there to see if the pharmacist catches the mistake
- Try to avoid preparing any pediatric doses in the future because they are just too scary



Pediatric Medication Safety

- Dose measurement errors
- Dose calculation errors



Dose Measurement Errors

- Small dose volumes can increase risk of filling errors
- 10-fold errors can have deadly results
- Double-check all doses prepared for pediatric patients
 - Right medication
 - Right concentration
 - Right dose



Dose Calculation Errors

- Wrong weight
 - Pounds vs kilograms
- Wrong units
 - Milligrams vs grams
 - Mg/kg/day vs mg/kg/dose
- Wrong frequency
- Please notify a pharmacist if a dose seems abnormal



Case

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- A. Ridicule the new tech in front of all the pharmacy staff to assure this mistake never happens again
- B. Leave the dose there to see if the pharmacist catches the mistake
- C. Try to avoid preparing any pediatric doses in the future because they are just too scary



Take-Home Points

- Pediatric patients require unique dosage forms for a variety of different reasons
 - Unique disease states
 - Unique toxicities
- Pediatric patients may be at risk for medication errors
 - Wrong concentration
 - 10-fold errors
 - Dose calculation errors
- Medication safety is EVERYONE'S job!!



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