Diuretics are commonly used in the Neonatal Intensive Care Unit to remove excess extracellular fluid secondary to various diseases such as bronchopulmonary dysplasia, chronic lung disease and acute kidney. Neonatal kidneys continue to develop after birth and are vulnerable to injury. There are many potential side effects that need to be closely monitored with diuretic use in the neonate. Cautious use is recommended.

Diuretics, NICU, AKI, Bronchopulmonary dysplasia, chronic lung disease

Diuretic Use in Neonates

Purpose and Goal: CNEP # 2082

- Learn about the use of diuretics in neonates
- Learn about adverse effects that occur with diuretic use

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Requirements for successful completion:

- Successfully complete the post-test
- Complete the evaluation form

Date
Learning Objectives

• Describe the way diuretics work in the neonate
• Describe the side effects of diuretic use in the neonate
• Describe at least 2 diagnoses that benefit from diuretic use

Introduction

• Diuretic use in common in high-risk NICU infants
  • It is a controversial management strategy
  • They are the most commonly ordered drugs
  • Furosemide is the 7th most common drug
  • Up to 8% of NICU infants receive diuretics
  • Up to 37% of preterm infants receive diuretics
    • Less than 32 weeks gestation
• Diuretics are used for several reasons:
  • To remove excess extracellular fluid
  • Secondary to various diseases
    • Chronic lung disease
    • Bronchopulmonary dysplasia
    • Congestive heart failure
• There is very limited data supporting their use
• But unwanted fluid retention can complicate optimal care
  • Diuretic action is ultimately guided by kidney function
  • Diuretic side effects can compromise optimal care
• There is a delicate balance between:
  • Diuretic related improvement
  • Diuretic related negative side effects
Diuretic Agents Used in Neonates

- Diuretics are delivered to the kidney in arterial blood
- All diuretics must reach the renal tubular lumen
  - Except for Spironolactone
- Optimal use of diuretics requires knowledge of:
  - Renal development
  - Renal physiology
  - Renal function
- A lower renal blood flow in preterm infants
  - Lowers the amount delivered to the kidneys
  - Potentially limits the effectiveness of the drugs
- There are several types of diuretics used in the NICU
  - Loop diuretics
  - Thiazides
  - Spironolactone
- Loop diuretics alter sodium reabsorption
- Thiazides also alter sodium reabsorption
- Spironolactone is an aldosterone antagonist

Development of the Renal System

- Nephrons continue development until 34 weeks
  - In the fetus and the preterm infant
- By 34 weeks the number of nephrons are similar to adults
- The nephrons continue to mature and grow into infancy
- Full functional development is not complete until 1-2 years
- The renal system passes through 3 stages of development
  - The first stage of development
    - Characterized by development
      - Of paired tubules
        - The paired tubules are nonfunctional
  - The second stage of development
    - Characterized by development
- Of glomeruli and tubules
  - The glomeruli and tubules can form urine
- The third stage of development
  - Characterized by development
    - Of renal tubular function
  - Occurs by the 12th week of gestation
  - This continues up to 34-36 weeks
- During the last trimester of gestation
  - Renal vasculature resistance is elevated
  - Fetal kidneys receive only 2-4% of blood flow
- Renal vasculature resistance falls after birth
  - Which leads to increased renal blood flow
  - Newborn kidney receives 8-10% of blood flow
  - This increases to 15-18% by a few months
  - This increases to 25% by adulthood
- Other changes occur with increased renal blood flow
  - Glomerular filtration rate is increased
    - Increases 50% during the first day of life
    - Doubles by 2 weeks of age in term infants
  - Renal sodium reabsorption is increased
- Glomerular filtration rates correlate with gestational age
  - Renal development continues after birth
  - Renal function is immature in preterm infants
  - Renal function does not mature faster with birth

**Functioning of the Renal System**

- All drugs must reach their site of action to be effective
- The site of action for diuretics is the kidney
- The nephron is the functional unit of the kidney
- The nephron is made up of:
  - The glomerulus
• The tubules
• The Bowman’s capsule

• Kidney function includes several processes
  • Secretion
  • Reabsorption
  • Excretion

• Protein-free filtrate is formed at the glomerulus
• The filtrate then moves through the proximal tubule
  • Large amounts of
    • Sodium
    • Chloride
    • Water
  • Are reabsorbed into the capillaries
  • Other substances are also reabsorbed
    • Glucose
    • Bicarbonate
    • Phosphate
    • Amino acids

• The filtrate then moves to the loop of Henle
  • More sodium is reabsorbed
• The filtrate then moves to the distal tubule
  • More sodium is reabsorbed
  • More chloride is reabsorbed
  • Sodium is exchanged for potassium

• The filtrate then moves to the collecting duct
  • This is the last site for reabsorption
• Finally, the filtrate is excreted as urine
• Neonates have renal differences as compared to adults
  • Increased excretion of sodium
  • Decreased ability to reabsorb glucose
  • More tubular proteinuria
  • Relative metabolic acidosis

• Neonates are at higher risk of abnormal renal function
Sodium and Chloride Reabsorption in the Kidney

- Sodium and chloride reabsorption occur at 4 sites
  - The proximal tubule (50-70%)
  - The loop of Henle (25-30%)
  - The distal tubule (5%)
  - The collecting duct (3%)
- The proximal tubule and loop of Henle
  - Reabsorb a large amount of sodium
  - To maintain consistency in the body
- The distal tubule and collecting duct
  - Maintain a fine balance of sodium
- The proximal tubule also drives:
  - The active transport of sodium
  - The passive transport of water
  - The passive transport of chloride
- The transport systems are highly interdependent
  - Disruption in sodium and chloride reabsorption
  - Directly affects water reabsorption
- Different types of diuretics target different areas
  - They target different transport systems
    - They block sodium reabsorption
    - They block chloride reabsorption
    - They block water reabsorption

Loop Diuretic Use in Neonates

- Loop diuretics act on the loop of Henle
- They are characterized by quick onset of action
- They are short acting with short duration of effect
• Mannitol
• Amiloride
• Torsemide
• Bumetanide
• Furosemide

• Furosemide is loop diuretic commonly used
  • Furosemide is also known as Lasix
  • Lasix increases blood flow to the kidneys
  • It acts to inhibit reabsorption:
    • Of sodium
    • Of chloride
    • Of potassium
  • It is primarily eliminated
    • In urine
    • As unchanged drug
    • Plasma clearance is low
  • The half-life is 24 hours in preterm infants
  • The half-life is 4 hours in term infants

• Repeated administration of loop diuretics
  • Produces drug tolerance
  • Results in distal tubular hypertrophy
  • Results in decreased effectiveness

• Prompt diuresis often results with furosemide
  • This can lead to hypotension
  • Fluid restricted infants are at greatest risk

Thiazide Diuretic Use in Neonates

• Thiazide diuretics are sulfonamide derivatives
  • Chlorothiazide
  • Chlorthalidone
  • Hydrochlorothiazide
  • Indapamide
• Metolazone
• Chlorothiazide is the thiazide commonly used
• Chlorothiazide is also known as Diuril
• Thiazide diuretics act on the distal tubule
• The exact mechanism of action is unknown
  • Thiazides tend to bind chloride
  • Which interrupts the transport of sodium
• Thiazides do not increase urinary calcium loss
  • They increase distal tubule calcium reabsorption
  • There is no risk of renal calcification
• When administered along with sodium supplements
  • There is decreased risk of hypocalcemia
• Thiazides are safe for long-term use in neonates

Spironolactone Use in Neonates

• Spironolactone is a synthetic steroid
  • It is a weak diuretic
  • It is also known as Aldactone
• It acts as an aldosterone receptor antagonist
  • Aldosterone is secreted by the adrenal glands
    • In response to decreased intravascular volume
• It also acts on the distal tubule and collecting duct
  • It increases the reabsorption of sodium
    • In exchange for potassium and hydrogen
• It is rapidly metabolized but slowly eliminated
• There are two aldosterone antagonists
  • Eplerenone
  • Spironolactone
• Spironolactone is the agonist commonly used
• Spironolactone is a potassium sparing diuretic
  • It is primarily used for this effect
• It is often used in combination with Chlorothiazide

Choosing Appropriate Diuretic Therapy

• When selecting appropriate diuretic drugs
  • Several factors should be considered
• Loop diuretics are most effective for diuresis
  • They are most effective at fast diuresis
  • But many adverse side effects can occur
  • They are safest for short-term use
• The role of thiazides is mostly adjunctive
  • To avoid side effects of furosemide
  • To treat furosemide dosing resistance
  • To prevent the development of calcifications
  • They may be used long-term as needed
• Aldosterone antagonists are also mostly adjunctive
  • They are best used in combination with thiazides
    • To increase potassium levels

Parameters to Monitor During Diuretic Therapy

• It is important to closely monitor several parameters
• Parameters that should be routinely monitored include:
  • Serum electrolytes
    • Sodium
    • Chloride
    • Potassium
    • Bicarbonate
    • Calcium
    • Magnesium
    • Glucose
- Renal function
  - Urine output
  - Serum creatinine
  - Blood urea nitrogen
  - Crystalluria
- Fluid balance
  - Intake
  - Output
  - Weight
- Blood pressure
- Hearing screen
- Other parameters
  - Serum uric acid concentrations

**Adverse Effects of Diuretic Therapy**

- Diuretic therapy is not without adverse side effects
- Electrolyte imbalance is the most common side effect
- Commonly seen adverse effects include:
  - Ototoxicity
  - Persistent PDA
  - Electrolyte imbalances
    - Hyponatremia
    - Hypokalemia
    - Hypocalcemia
    - Hypomagnesemia
    - Hypochloremia metabolic acidosis
  - Renal calcifications
- Because significant amounts of calcium are reabsorbed
  - Careful attention is critical
    - Hypercalciuria
    - Bone demineralization
• Renal calcifications
• Large dose or long-term use of Furosemide is well known:
  • To be associated with renal calcifications
  • >10 mg/kg/day can cause nephrocalcinosis
• To be associated with persistent PDA
• To be associated with irreversible ototoxicity
• If serum calcium levels are affected long-term
  • Parathyroid hormone secretion is affected
  • Which can lead to bone demineralization
  • Left untreated metabolic bone disease can occur

Diuretic Use in Bronchopulmonary Dysplasia

• Bronchopulmonary dysplasia
  • Is also known as chronic lung disease
  • It is a common cause of NICU complications
    • It results in significant morbidity
    • It results in significant mortality
• Day-to-day care is focused on improving symptoms
• Many interventions have little impact on long-term outcomes
• BPD is associated with severe respiratory distress syndrome
• It is characterized by:
  • Long-term oxygen requirement
  • Interrupted lung development
    • Decreased septation
    • Alveolar hypoplasia
    • Reduced surface area of gas exchange
  • Airway injury and subsequent inflammation
    • Which leads to pulmonary edema
  • Abnormal development of pulmonary vasculature
    • Abnormal distribution of capillaries
    • Thickening of muscle layer of arterioles
• Long-term pulmonary complications
• Poor neurodevelopmental outcomes
• Most neonates with BPD improve slowly over time
  • Depending on speed of healing
  • Depending on rate of lung growth
• Management of BPD is aimed at minimizing further injury
  • Long-term diuretic therapy may be beneficial
  • Fluid restriction may avoid pulmonary edema
  • Adequate nutrition is critical for proper growth
• The goal of diuretic therapy in BPD is to:
  • Counteract fluid retention
  • Improve pulmonary function
  • Assist the reabsorption of interstitial edema
• Two classes of diuretics are commonly used in BPD
  • Loop diuretics
  • Thiazide diuretics
• Diuretic use causes urinary loss
  • Sodium
  • Potassium
  • Chloride
• Diuretic use also causes electrolyte imbalances
  • Hyponatremia
  • Hypokalemia
• Dietary supplementation is needed
  • Sodium chloride
  • Potassium chloride
• Hyperchloremic alkalosis is a frequent complication
• Blood gases and electrolytes should be closely monitored

Diuretic Use in Acute Kidney Injury

• Acute kidney injury is also known as AKI
• AKI is observed in 3-24% of NICU infants
• Risk factors for AKI include:
  • Critically ill term infants
  • Critically ill preterm infants
  • Low birthweight infants
  • Very low birthweight infants
  • Additional risk factors:
    • Hypotension
    • Hypovolemia
    • Hypoxia
    • Persistent PDA
    • Nephrotoxic drugs
• AKI is described as the abrupt decrease in renal function
  • Over a period of days to hours
  • Resulting in failed excretion of urine
  • Leading to nitrogenous waste retention
  • Leading to failure to maintain electrolyte balance
  • Leading to failure to maintain fluid balance
• Up to 79% of preterm infants may be diagnosed with AKI
• Preterm infants are at higher risk due to:
  • Intrauterine growth restriction
  • Maternal medications
    • NSAIDs
    • Infections
    • Antibiotics
    • Placental insufficiency
  • The rate of mortality is 10-61%
• Preterm kidneys are structurally and functionally immature
• Altered kidney function leads to fluid retention
  • Which is also common in renal disease
  • Which is also common in pulmonary disease
• The goal of diuretic therapy in AKI is to:
  • Improve urine output
• Maintain fluid and electrolyte balance
• Prevent fluid and electrolyte imbalance
• Two loop diuretics are commonly used in AKI
  • Furosemide
  • Bumetanide
• Loop diuretics limit and prevent volume overload
• They are known to potentiate pre-existing problems
• Monitoring and correction is critical prior to use
  • Hypotension
  • Fluid balance
  • Significant acidosis
• Diuretics are used to convert oliguric AKI \(\rightarrow\) non-oliguric AKI
• Blood gases and electrolytes should be closely monitored

Summary

• Diuretics are commonly used in the NICU
• They are among the most frequently ordered drugs
• They are used to prevent and treat fluid retention
• It is important to understand several principles
  • Appropriate use of diuretics
  • Possible harmful side effects of diuretics
  • Proper monitoring for side effects
• Diuretics should be used cautiously in the NICU
• Their benefits should be carefully weighed against the risks

References


