Objectives

1. Describe the basic pathophysiology of cystic fibrosis & the organs affected
2. List two differences in drug metabolism in CF patients
3. Briefly discuss the medications utilized in CF
Cystic Fibrosis Module #1: An Overview for Pharmacists

What is CF?

• Inherited chronic disease that affects the lungs and digestive organs
• Affects ~70,000 worldwide (peds & adult)
  – ~30,000 in U.S.
• Defect gene & protein product leads to:
  – Thick sticky mucus that clogs:
    • Lungs and airways
    • Blocks release of pancreatic enzymes

CF Symptoms for Diagnosis

• Skin that tastes salty
• Persistent (sometimes productive) cough
• Frequent infections in lung
• Wheezing or shortness of breath
• Failure to thrive (i.e. poor weight/height gain)
• Greasy/oily stools
• Frequent constipation
Pathophysiology

- Autosomal recessive disorder caused by mutations in a gene located on chromosome 7
- Gene encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) channel


Pathophysiology

- >1000 disease-association mutations may occur to the CFTR gene
- Classified according to the mechanism in which they cause disease
  - Categories I-VI

Pathophysiology

• Most common mutation is called ∆F508 (no phenylalanine at position 508)
  – Occurs in 90% of CF patients in U.S.
• ∆F508 is considered a class II
  – Mutation results in misfolded CFTR protein
  – Gets degraded


Pathophysiology

• CFTR is involved with the maintenance of fluid balance across epithelial cells
• Mutations in CFTR gene result in defective chloride transport in epithelial cells

Pathophysiology

• ↓ Cl⁻ transport + ↓ Na⁺ transport + ↓ H₂O transport = dehydrated, viscous secretions
• Thick secretions = obstruction, destruction, and scarring of exocrine ducts


Pathophysiology

• Thick duct secretions lead to:
  – Pancreatic insufficiency
  – Lipid malabsorption
  – Constipation
  – Cystic Fibrosis Related Diabetes (CFRD)
  – Obstructive biliary disease

Pathophysiology

- Thick duct secretions lead to:
  - Azoospermia in males
  - Obstructive pulmonary disease
  - Bronchiectasis
  - Chronic pulmonary infections


Drug Pharmacokinetics in CF

- Absorption
  - Rate—slower; Extent varies = no affect on bioavailability of oral medications

- Distribution
  - No difference in plasma protein binding
  - Vd not affected w/ most drugs
    - Increased in antibiotics (ceftazidime, gentamicin) & theophylline

Drug Pharmacokinetics in CF

- Metabolism (hepatic)
  - *↑*d for many drugs
    - Ex: Ciprofloxacin, Furosemide, Sulfamethoxazole/Trimethoprim, Ibuprofen, Lorazepam, Acetaminophen, Theophylline, Warfarin

- Elimination
  - *↑*d for many drugs
    - Ex: Amikacin, Ceftazidime, Ticarcillin, Trimethoprim

Areas Where Drug Therapy Exists

- Cystic Fibrosis
- Gastrointestinal
- Endocrine
- Pulmonary
Pancreatic Enzymes

• Contain lipase, protease, and amylase
• Necessary for absorption of fats, proteins and fat soluble vitamins
• Decrease steatorrhea and other GI complaints
• Appropriate weight gain

Pancreatic Enzymes

• FDA approved enzymes on market
  – Creon®, Zenpep®, Generic Zenpep®, Pancreaze®, Viokase®, Ultresa®, Pertzye®
• Per CFF recommendations
  – No generic pancreatic enzymes should be used based on variability of product and safety/efficacy issues
Pancreatic Enzyme Dosing

<table>
<thead>
<tr>
<th>Age</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (breast-fed)</td>
<td>2000-4000 units lipase/feeding</td>
</tr>
<tr>
<td>Infants (bottle-fed)</td>
<td>2000-4000 units lipase/120 ml feeding</td>
</tr>
<tr>
<td>1-4 years</td>
<td>1000 units/kg lipase/meal 500 units/kg lipase/snack</td>
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<tr>
<td>&gt; 4 years</td>
<td>500 units/kg lipase/meal 250 units/kg lipase/snack</td>
</tr>
</tbody>
</table>


Pancreatic Enzymes

- Max dose 2500 units/kg lipase per meal or 10,000 units/kg lipase per day
- May increase dose if steatorrhea
  - 500 units/kg per meal every 3 days
- Decrease dose for constipation
- Overdose may lead to fibrosing colonopathy

Pancreatic Enzymes

- Each capsule contains many small beads – do not break or chew
- Not stable in milk or formula
- Pour contents of capsule onto a teaspoon of baby food or applesauce
- Check infant’s mouth to ensure no remaining beads


Acid Suppression Therapy

- Improves pancreatic enzyme efficacy
  - Decreased pancreatic bicarbonate secretion in CF patients
  - Leads to higher amounts of gastric acid
  - Pancreatic enzymes more effective when in a less acidic environment
  - Using PPI or H2 blocker may help reduce acid and improve enzyme efficacy

Digestive Therapy

- Vitamin Deficiency
  - ↓ pancreatic enzyme secretion → fat malabsorption → ↓ fat-soluble vitamin levels
  - Fat-soluble vitamins (A, D, E, K)
  - Levels should be monitored
  - Supplementation is essential

Yankaskas J et al. CHEST 2004; 125:1S–39S

Fat Soluble Vitamins

- Supplements: Aquadeks®, Vitamax®, Libertas®, MVW Complete Formulation®
  - Multiple vitamins with increased amounts A, D, E, & K

Yankaskas J et al. CHEST 2004; 125:1S–39S
Vitamins

• ADEK vitamins alone may not be sufficient
  – Levels monitored for efficacy
• Vitamins D and E levels commonly low
• Supplement Dosing:
  – Vit D 800-10,000 international units/day
  – Vit E 40-400 international units/day
  – Vit A 1500-10,000 international units/day
  – Vit K 0.3-5 mg daily to weekly

Digestive Therapy

• Vitamin Deficiency
  – Reasons to supplement
    • Night blindness (Vitamin A)
    • Hemolytic anemia (Vitamin E)
    • Bone disease (Vitamin D/K)
    • Bleeding disorders (Vitamin K)

Yankaskas J et al. CHEST 2004; 125:1S–39S
Constipation

- Distal intestinal obstruction (DIOS)
  - Causes
    - Abnormally viscous GI secretions
    - Fecal impaction
    - *Clostridium difficile* infection
  - Worsened by ingestion of a fatty meal or noncompliance with enzyme therapy

Yankaskas J et al. CHEST 2004; 125:1S–39S

Digestive Therapy

- Constipation
  - Docusate sodium = stool softener by reducing surface tension & ↑ water/fat into stool
  - Polyethylene glycol = osmotic agent—water retention in stool (↑ frequency/consistency)
  - Sennosides = stimulates peristalsis via irritation of intestinal muscle

Yankaskas J et al. CHEST 2004; 125:1S–39S
Hepatobiliary Disease

• Impaired chloride and water secretion at bile duct level
• Thickened secretions in bile ducts
  – Portal fibrosis
  – Cirrhosis

Hepatobiliary Disease

• Ursodiol
  – ↓ cholesterol content of bile by ↓ secretion of cholesterol from liver & absorption of cholesterol in intestines
  – Dose (children) = 30 mg/kg/day divided q 12 hours
  – Dose (adults) = 300 mg twice daily
Hepatobiliary Disease

- Vitamin K supplementation (phytonadione, Mephyton®)
  - Dose: 2.5-5mg twice weekly increasing up to 10mg daily depending on severity

- Taurine-amino acid which is a component of bile
- May improve fat absorption in small intestine
  - Study results are conflicting
- Dose: 30-40mg/kg/day (500-1500mg) daily to three times daily
  - Available as 500mg tabs
Digestive Therapy

- Non-pharmacological
  - Follow normal dietary pattern (no restrictions)
  - Energy dense foods
  - Calorie-dense oral supplements (i.e. Carnation Instant Breakfast, Pediasure)
  - Enteral feedings

Areas Where Drug Therapy Exists

- Cystic Fibrosis
  - Gastrointestinal
  - Endocrine
  - Pulmonary
Endocrine Therapy

- Cystic Fibrosis Related Diabetes (CFRD)
  - Very rare in CF children <10 years
  - ↑ incidence as patients get older
  - ~50% have CFRD at age 30 years
  - More common in patients w/ ΔF508 mutation

CFRD

- Associated with ↑ morbidity & mortality
- ↓ lung function
- ↓ BMI
- ↑ microvascular complications (retinopathy, nephropathy, neuropathy)
Cystic Fibrosis Module #1: An Overview for Pharmacists

CFRD Pathology

- **Pathogenesis:** Thickened secretions ➞ Fibrosis of pancreas ➞ Reduced beta cell function ➞ Decreased insulin secretion.
- Decreased insulin sensitivity in peripheral tissues
- Shares characteristics of both Type 1 & Type 2

Yankaskas J et al. CHEST 2004; 125:1S–39S

CFRD Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age @ onset (yrs)</td>
<td>&lt;20</td>
<td>&gt;40</td>
<td>18-21 (43%&gt;30 yrs)</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Normal</td>
<td>Obese</td>
<td>Thin</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>▼▼▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>▼</td>
<td>▼▼▼</td>
<td>▼</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Microvascular</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Macrovascular</td>
<td>Yes</td>
<td>Yes</td>
<td>??</td>
</tr>
</tbody>
</table>

Moran et al. Diabetes Care 2010; 33(12):2667-2683
CFRD

- Screening (begin @ age 10)
  - 2-hr 75-gram OGTT (begin @ age 10)--annually
  - Fasting @ 2-hr post-prandial glucose if admitting for IV Abx or receiving systemic glucocorticoids
- Diagnosis (stable)
  - FPG* >126mg/dL on two occasions
  - Random glucose ≥200mg/dL on two occasions
  - HgA1c ≥ 6.5%
  - 2-hr post-prandial glucose > 200mg/dL (After OGTT)
*FPG = Fasting Plasma Glucose

Moran et al. Diabetes Care 2010; 33(12):2667-2683

CFRD

- Diagnosis (acute exacerbation or systemic steroids)
  - FPG* >126mg/dL or
  - 2-hr post-prandial plasma glucose ≥ 200 mg/dL x 48 hrs
- Continuous feeds
  - Mid or post-feeding glucose ≥ 200 mg/dL x 48 hrs

Moran et al. Diabetes Care 2010; 33(12):2667-2683
Oral Glucose Tolerance Test (OGTT)

• Test Specifics:
  – Dose = 1.75gm/kg glucose (75gm max)
  – Consume quickly
  – Test glucose at 1 and 2 hrs after consumption
  – Tastes better if refrigerated

Moran et al. Diabetes Care 2010; 33(12):2667-2683

CFRD Monitoring & Treatment

• Insulin Therapy
  – Primarily for meal coverage
    • Use short acting insulin (Lispro or Regular) & Insulin Glargine (Lantus ®)
    • Carbohydrate counting important
  – Should individualize for pt’s needs & lifestyle
    • No dietary restriction
• Monitor Blood glucose 3 x’s/day
• HgA1c quarterly
• Oral hypoglycemics
  – Not recommended

Moran et al. Diabetes Care 2010; 33(12):2667-2683
Cystic Fibrosis Module #1: An Overview for Pharmacists

Areas Where Drug Therapy Exists

- Cystic Fibrosis
  - Gastrointestinal
  - Endocrine
  - Pulmonary

Pulmonary Pathogenesis

- Primary cause of morbidity & mortality
  - ~90% of fatalities
- Hypotheses have been proposed to explain the pulmonary pathogenesis
- Steps have been recognized as targets for therapeutic interventions

Flume et al., Am J Respir Crit Care Med 2009; 180:802–808
Defective CF gene $\rightarrow$ Defective CFTR $\rightarrow$ Thick viscous secretions $\rightarrow$ Bronchial Obstruction $\rightarrow$ Activation of airway inflammatory cells (PMNs) $\rightarrow$ Infection $\rightarrow$ Inflammation $\rightarrow$ Bronchiectasis

Targets of Existing Therapy

Nonpharmacologic
Chest physiotherapy, Vest

Thick viscous secretions $\rightarrow$ Bronchial Obstruction $\rightarrow$ Activation of airway inflammatory cells (PMNs) $\rightarrow$ Infection $\rightarrow$ Inflammation $\rightarrow$ Bronchiectasis
Pulmonary Therapy

- Nonpharmacologic techniques
  - Chest physiotherapy
  - Vest

Order of CF Medications

1. Bronchodilator
2. Hypertonic saline
3. Dornase alfa
4. Inhaled antibiotic
5. Inhaled corticosteroid
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Targets of Existing Therapy

Bronchodilators
- Albuterol, Levalbuterol, Salmeterol, Formoterol, Arformoterol, Indacaterol

Thick viscous secretions

Bronchial Obstruction

Activation of airway inflammatory cells (PMNs)

Infection

Inflammation

Bronchiectasis

Targets of Existing Therapy

Mucolytics
- Dornase alfa, Hypertonic saline

Thick viscous secretions

Bronchial Obstruction

Activation of airway inflammatory cells (PMNs)

Infection

Inflammation

Bronchiectasis
Cystic Fibrosis Module #1: An Overview for Pharmacists

Thick viscous secretions
Bronchial Obstruction
Activation of airway inflammatory cells (PMNs)
Inflammation
Bronchiectasis

Targets of Existing Therapy

Antimicrobials
Inhaled tobramycin;
Inhaled aztreonam;
IV antibiotics

Infection

Anti-inflammatory
Ibuprofen,
Azithromycin, Inhaled,
nasal corticosteroids

Inflammation

Bronchiectasis
Cystic Fibrosis Module #1: An Overview for Pharmacists

Conclusions

- Cystic fibrosis is a very complex genetic disorder
- Morbidity & mortality are high, but improvements are being made
- Treatments exist to alleviate symptoms & modify the disease process