Pancreatic Enzyme Insufficiency

Introduction

Pancreatic enzyme insufficiency (PEI) involves the failure of the pancreas to secrete digestive enzymes. The condition can range from mild insufficiency to complete pancreatic exocrine failure. In the most extreme cases, it causes steatorrhea, failure to absorb fat-soluble vitamins, diarrhea, weight loss, malnutrition, and failure to thrive in infants.

PEI is not a disease but a condition that can result from a number of diseases or from damage to the pancreas. Diseases associated with PEI cause loss of the pancreatic parenchyma, which leads to insufficient secretion of enzymes. Among the diseases associated with PEI are cystic fibrosis, chronic pancreatitis, severe acute pancreatitis, and pancreatic duct obstruction from tumors. In addition, PEI is associated with diabetes, celiac disease, inflammatory bowel disease, Sjogren’s syndrome, polyarthritis, HIV infection, and rare genetic disorders including Shwachman-Diamond syndrome, Pearson’s marrow-pancreas syndrome, and Johanson-Blizzard syndrome. PEI may result from surgical operations such as gastric bypass, gastrectomy, and pancreatectomy.

It is estimated that PEI affects 880,000 worldwide. Because several diseases are associated with PEI, the number of people potentially at risk for PEI is large (see table below).

Estimated of Numbers of People at Potentially at Risk for PEI in the United States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>35,000 (prevalence)</td>
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<tr>
<td>Acute Pancreatitis</td>
<td>210,000 cases/year</td>
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<tr>
<td>Pancreatic Cancer</td>
<td>38,000 cases/year</td>
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<td></td>
<td>34,000 deaths/year</td>
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<tr>
<td>Diabetes</td>
<td>23.6 million (prevalence)</td>
</tr>
<tr>
<td>IBD (including ulcerative colitis and Crohn’s disease)</td>
<td>459,000 (prevalence)</td>
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<tr>
<td>Celiac disease</td>
<td>2.3 million (prevalence)</td>
</tr>
<tr>
<td>Sjogren’s Syndrome &amp; Polyarthritis</td>
<td>4 million (prevalence)</td>
</tr>
<tr>
<td>HIV</td>
<td>1.1 million (prevalence)</td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome</td>
<td>4,100 (prevalence)</td>
</tr>
<tr>
<td>Pearson’s Syndrome</td>
<td>Extremely rare</td>
</tr>
</tbody>
</table>

Pathophysiology of PEI

The acinar cells of the pancreas secrete several enzymes involved in digestion, the major ones being amylase, protease, and lipase, which are responsible for digesting starch, proteins, and fats, respectively. The absence or an inadequate quantity of these enzymes inhibits absorption of essential vitamins and nutrients. Inadequate secretion of pancreatic enzymes occurs due to damage to the acinar cells or ductal obstruction.
Malabsorption of fats is a central feature of PEI. Due to the large functional reserve of the pancreas, however, a loss of 90% of normal levels of postprandial secretion may occur before malabsorption of fats occurs.\(^8,9\) Therefore, steatorrhea may not occur until the second or third decade after onset of symptomatic disease. Steatorrhea occurs earlier in PEI associated with excess alcohol consumption. Stools with high fat content are likely to be frothy, foul-smelling, and oily.\(^2\) In addition, absorption of the fat-soluble vitamins A, D, E, and K is likely to be impaired.

Poor digestion of fat is a greater issue than digestion of carbohydrates and protein. This is due to the fact that lipase is inactivated at a pH of 5 and lower whereas the other digestive enzymes are not as greatly affected by pH.\(^8\) In many cases of PEI, the pancreatic duct cells fail to secrete bicarbonate. Failure to neutralize chyme results in impaired lipid solubilization further inhibiting digestion and absorption of lipids. Low pH in the duodenum also leads to precipitation of bile acids, which also impairs digestion of lipids.\(^10\) Typically in PEI, most digestion occurs in the lower intestine where it is not optimal. Very little intact lipase reaches the distal small intestine.\(^9\) The presence of incompletely digested material at this point causes inhibition of gastrointestinal secretions and motility.

In the case of cystic fibrosis, abnormalities in the protein produced by the cystic fibrosis transmembrane regulator (CFTR) gene cause duct obstruction and destruction of acinar cells.\(^10\) The defective protein causes abnormal movement of fluids and electrolytes. This can alter uptake and transport of long-chain fatty acids. It can also alter intestinal motility increasing transit time in the small bowel.

**Pancreatic Enzyme Replacement Therapy (PERT)**

**Generic PERT and FDA NDA Process**

The development of pancreatic enzyme replacement therapy (PERT) occurred before the passage of the Federal Food, Drug, and Cosmetic Act in 1938.\(^11\) As a consequence, several PERT medications were grandfathered and testing did not follow current standards. These grandfathered medications are sometimes referred to as generic PERT. This terminology differs from the usual understanding of the term “generic.”

The enzymatic activity was not equivalent among these “generic” drugs, making selection and determination of appropriate dosing difficult. In 2004, the FDA required all makers of PERT medications to participate in the new drug approval process to standardize enzyme activity. Originally, PERT medications were required to apply for the new drug approval by April of 2008. The FDA has since extended this deadline to April 28, 2010.

**PERT Dosing**

PERT medications are formulated as acid-resistant, pH-sensitive microspheres to resist the acidic conditions of the stomach.\(^8\) The most efficacious microsphere size appears to
be in the range of 1.0 to 1.2 mm in diameter.\textsuperscript{3} PERT medications must be taken during meals to be effective.

Dosing recommendations are not standardized. Some recommendations are in units of lipase per meal, others in units per kilogram of body weight per meal, and yet others in units per gram of dietary fat per day (see table).

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommended Dosage of Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. Layer and J. Keller, 2003\textsuperscript{8}</td>
<td>25,000 – 40,000 IU/meal; may be increased not to exceed 75,000 IU/meal</td>
</tr>
<tr>
<td>P. Layer, J. Keller, P.G. Lankisch\textsuperscript{9}</td>
<td></td>
</tr>
<tr>
<td>J.E. Dominguez-Munoz, 2007\textsuperscript{7}</td>
<td>30,000 IU/meal</td>
</tr>
<tr>
<td>Stallings et al., 2008\textsuperscript{12}</td>
<td>For cystic fibrosis: 500 – 2,500 units/kilogram body weight per meal; &lt; 10,000 units/ kilogram body weight per day; &lt; 4,000 units/gram dietary fat per day</td>
</tr>
</tbody>
</table>

Typically, it is recommended that dosing start at a lower level and increased if steatorrhea is not corrected.\textsuperscript{8} Normally, the postprandial secretion of lipase of 25,000 to 40,000 IU is required to digest a meal and this amount should be considered the starting point for proper dosing. If this dose is not adequate, the dose can be increased two to three times and/or five to six smaller meals should be distributed throughout the day. Doses greater than 75,000 IU of lipase per meal are not recommended due to the potential for fibrosing colanopathy. If successful dosing is not achieved, the fat content of meals should be reduced. If steatorrhea continues to be a problem, it may be necessary to test patient adherence to medication through fecal chymotrypsin testing. The next step in treatment is the use of proton pump inhibitors or H\textsubscript{2}-blockers. If treatment is still unsuccessful, the other possibilities such as giardiasis, bacterial growth from surgery, or other intestinal absorption disorders should be investigated.

### Adverse Events and Potential Drug Interactions

There are several adverse events that can be associated with PERT, which health care providers should be aware of. Extremely high doses of PERT can cause fibrosing colanopathy.\textsuperscript{9} Doses exceeding 75,000 IU of lipase per meal are not recommended. Older, less pure extracts of pancreatic enzymes could cause hyperuricemia and hyperuricosuria, but these problems are not seen with the modern, microsphere formulations.\textsuperscript{10} If powered preparations are taken or acid-resistant microspheres are chewed or dissolved in the mouth, soreness of the mouth can occur. Perianal irritation is possible if there is significant proteolytic enzyme activity in stools. Patients who are allergic to pork may have allergic responses to PERT medications since they are derived from hogs. Too rapid an increase in dose may cause severe constipation and abdominal pain.

The effectiveness of pancreatic enzymes may be reduced when taken with calcium or magnesium containing antacids.\textsuperscript{13} In addition, the enzymes may affect the effectiveness of some diabetic medications and there may be interactions with iron supplements.
**Future Directions**

Bacterial formulations of lipase have been found in animal experiments to be as much as 75 to 100 times more effective than porcine lipases.\(^8,9\) In addition, bacterial lipase is stable in moderately acidic and neutral environments. These formulations are not inactivated by bile salts. Interestingly, bacterial lipases have been shown in animals to increase efficacy with increasing amounts of dietary fat. Further testing in humans is necessary.

**Needs Assessment**

Several issues related to PEI and PERT call for rigorous continuing medical education. These issues include PEI being associated with numerous medical conditions, complex pathophysiology, changes in FDA PERT regulation, a complex dosing strategy, and significant adverse effects and drug-drug interactions associated with PERT.

Pancreatic exocrine insufficiency is a condition that is more common than providers are aware. Numerous, highly prevalent diseases as well as surgical procedures are associated with PEI. **Review of the diseases and surgical procedures associated with PEI will ensure that providers accurately identify PEI and ensure appropriate treatment is provided in a timely manner.**

The pathophysiology of PEI is complex, involving issues related to production and secretion of enzymes that are influenced by changing gastrointestinal pH and location of digestive processes within the gastrointestinal tract. In addition, the secretion of bicarbonate may be impaired as well as the secretion of the pancreatic enzymes themselves. **A thorough review of lipase production, secretion, and gastrointestinal tract factors will give providers an understanding of complexity of the system and the functioning of pancreatic enzymes in both healthy persons and patients with PEI.**

The FDA has recently addressed the use of grandfathered PERT medications, requiring that they follow NDA procedures. In addition, PERT medications are not equivalent and cannot be interchanged. Due to the use of the term “generic”, PERT medications may be incorrectly considered equivalent and in fact, Inman and Milavetz describe a case in which a patient’s prescription was substituted with another “generic” product with significant adverse effect.\(^4\) **Review of the history of PERT medications and the recent FDA changes with respect to PERT medication will ensure that providers are aware of the changing status of PERT medications and also ensure that medications are not substituted inappropriately.**

It is critical that determination of dosing follow a procedure that adequately treats patients without inducing adverse effects. **Review of a safe method for assessing appropriate dosing will ensure that patients are adequately treated while avoiding potential adverse effects.**

PERT medications have the potential for serious adverse effects including fibrosing colonopathy. In addition, there is the potential for significant drug-drug interactions with PERT medications. **Review of the potential adverse effects and drug-drug interactions**
associated with PERT will ensure that providers properly treat patients and avoid serious negative impacts.

<table>
<thead>
<tr>
<th>Educational Gap</th>
<th>Data Source</th>
<th>Intervention</th>
<th>Learning Objectives</th>
<th>Outcomes Measurement Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providers are not aware that PEI is a risk factor associated with several conditions.</td>
<td>Conwell et al.²</td>
<td>Identify the full range of conditions that are associated with PEI and the prevalence of each condition.</td>
<td>Review conditions, which place patients at risk of PEI so that providers recognize when it is appropriate to test for PEI.</td>
<td>3/4/5 (Knowledge/Competence/Performance)</td>
</tr>
<tr>
<td>Providers are not familiar with the pathophysiology of PEI.</td>
<td>Inman and Milavetz⁴</td>
<td>Review healthy pancreatic physiology and PEI pathophysiology.</td>
<td>Review the history of PERT medications and FDA rationale for NDA status so that providers are aware that PERT medications are not interchangeable.</td>
<td>3/4/5 (Knowledge/Competence/Performance)</td>
</tr>
<tr>
<td>Providers are not aware of the recent changes in FDA PERT regulation and that different formulations are not equivalent.</td>
<td></td>
<td>Review the recent FDA actions with respect to PERT and the history of PERT medications.</td>
<td>Review the history of PERT medications and FDA rationale for NDA status so that providers are aware that PERT medications are not interchangeable.</td>
<td>3/4/5 (Knowledge/Competence/Performance)</td>
</tr>
<tr>
<td>Providers are not aware of the technique for determining appropriate PERT dosing for patients.</td>
<td></td>
<td>Review the practice for determining the appropriate patient PERT dosing.</td>
<td>Discuss the methods of determining PERT dosing to reduce steatorrhea in such a way that patients do not suffer adverse effects.</td>
<td>3/4/5 (Knowledge/Competence/Performance)</td>
</tr>
<tr>
<td>Providers are not familiar with adverse effects and drug</td>
<td></td>
<td>Present the possible adverse effects and drug interactions associated with PERT therapy.</td>
<td>Identify the potential adverse effects and drug interactions associated with PERT to ensure that</td>
<td>3/4/5 (Knowledge/Competence/Performance)</td>
</tr>
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Learning Objectives

- Review conditions, which place patients at risk of PEI so that providers recognize when it is appropriate to test for PEI.
- Discuss pancreatic enzyme physiology in healthy persons and PEI pathophysiology so providers understand the conditions under which PEI occurs and are equipped to provide appropriate care.
- Review history of PERT medications and FDA rationale for NDA status so that providers recognize these medications are not interchangeable.
- Discuss methods of determining PERT dosing to reduce steatorrhea in such a way that patients do not suffer adverse effects.
- Identify the potential adverse effects and drug interactions associated with PERT to ensure that patients are appropriately treated and adverse events avoided.

Proposed Agenda

I. Introduction
II. Conditions Associated with PEI and Prevalence Rates
III. Role of Pancreatic Enzymes
   - Healthy Function
   - Pathophysiology
IV. History of PERT Medications and Changes in FDA Regulation
V. PERT Dosing
   - Strategy for Determining Dose
   - Costs Associated with PERT
VI. Adverse Events & Drug-Drug Interactions
VII. Case Study
References