Treatment of Pancreatic Exocrine Insufficiency with Enteric Coated Pancreatin Formulations: An Overview

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ABSTRACT

Pancreatin is a mixture of several digestive enzymes produced by the exocrine cells of the pancreas. It is composed of amylase, lipase and protease. It is used to treat conditions in which pancreatic secretions are deficient, such as surgical pancreatectomy, pancreatitis and cystic fibrosis. Pancreatin products contain the pancreatic enzymes trypsin, amylase and lipase. The patients with pancreatic diseases often suffer from pancreatic exocrine insufficiency. In such condition pancreas does not secrete required amount of digestive enzymes for proper digestion to occur. Severe pancreatic insufficiency occurs in cystic fibrosis, chronic pancreatitis, tumors or after surgical resection. Thus pancreatic exocrine insufficiency may result in clinical manifestation of malnutrition, weight loss and steatorrhea leading towards the increased risk of morbidity and mortality. For the improvement of clinical symptoms, restriction of fat intake and pancreatic enzyme replacement therapy are recommended. The enzyme substitution therapy is very much challenging because the optimal enzyme dose is highly variable to mimic the physiological pattern of pancreatic exocrine secretion. Regulatory authorities have approved several pancreatic enzyme formulations in the form of enteric coated minimicrosphere which are now available commercially. This review focuses on the physiological considerations of pancreatic exocrine insufficiency and its treatment with enteric coated pancreatin formulations.

KEYWORDS: Pancreatic exocrine insufficiency, fat digestion, enzyme replacement therapy, enteric coated pancreatin, minimicrosphere, dose.

Introduction

The physiological process for digestion of macronutrients is a prerequisite for absorption which occurs mostly via enzyme hydrolysis (Keller and Layer, 2005). For this purpose, pancreatic enzymes, specifically amylase, lipase, trypsin and chymotrypsin have the major contribution. Apart from digestive enzymes, pancreas also secretes water, bicarbonate into the duodenum. The pancreas is a retroperitoneal organ where capsular layer is lacking. The spleen is positioned adjacent to the pancreatic tail. Structurally pancreas is divided into head, body, tail and uncinate process region. Functionally pancreas is divided into exocrine portion (acinar and duct tissue) and endocrine portion (islets of Langerhans). The distal end of the common bile duct passes through the head of the pancreas and joins the pancreatic duct entering the duodenum (Pandol, 2010).

Pancreatin is a mixture of several digestive enzymes produced by the exocrine cells of the pancreas. It is composed of amylase, lipase and protease. This mixture is used to treat conditions in which pancreatic secretions are deficient, such as surgical pancreatectomy, pancreatitis and cystic fibrosis. Pancreatin products contain the pancreatic enzymes trypsin, amylase and lipase. The trypsin found in pancreatin works to hydrolyze proteins into oligopeptides; amylase hydrolyzes starches into oligosaccharides and the disaccharide maltose; and lipase hydrolyzes triglycerides into fatty acids and glycerols. Pancreatin reduces the absorption of iron from food in the duodenum during digestion (Smith, 1965). Pancreatin is an effective enzyme supplement for replacing missing pancreatic enzymes, and aids in the digestion of foods in cases of pancreatic insufficiency.

Pancreatic exocrine insufficiency is a major disease where pancreas is unable to deliver sufficient amount of digestive enzymes to small intestine. Comprehensive knowledge about physiology of pancreatic exocrine response to normal diets is necessary to diagnose the disease. As the pancreas has large residual capacity, the exocrine insufficiency becomes clinically apparent only when 90% of its function is lost (Lankisch et al., 1986b; Layer et al, 1986). Postoperatively exocrine insufficiency is observed in 65- 80% of the patients with chronic
physicians should be more focused on treating exocrine with a good number of populations in all the countries, (Sikkens et al., 2012). As this is a world wide problem highly variable. It depends upon the pancreatic function, highly challenging as the optimal dose of enzyme is pancreatic enzymes. This enzyme replacement therapy is insufficiency are treated with sufficient dose of mortality, patients suffering from pancreatic exocrine (Dominguez-Munoz, 2011).

In clinical practice, for the reduction of morbidity and mortality, patients suffering from pancreatic exocrine insufficiency are treated with sufficient dose of pancreatic enzymes. This enzyme replacement therapy is highly challenging as the optimal dose of enzyme is highly variable. It depends upon the pancreatic function, the post surgical anatomy and the dietary fat content (Sikkens et al., 2012). As this is a world wide problem with a good number of populations in all the countries, physicians should be more focused on treating exocrine insufficiency and educate patients to adjust dose in accordance with symptoms and their diet.

**Cascade of exocrine pancreatic secretion**

Human exocrine pancreatic secretion occur both during the fasting (inter digestive) state and after ingestion of a meal (digestive). This inter digestive pattern of secretion begins when upper gastrointestinal tract is cleared of food. In an individual who eats three meals per day, the digestive pattern begins after breakfast and continues until late in the day, after the evening meal is cleared from the gastrointestinal tract (Pandol, 2010).

**Inter digestive secretion**

The inter digestive secretion is a cyclic process in accordance with the pattern of MMC (DiMagno et al., 1979). This process is regulated by chronic nervous system (Zimmerman et al., 1992). The cycle recurs in after every 60 to 120 minutes. In addition to digestive enzyme secretion, there is increased secretion of bicarbonate and bile into the duodenum.

**Digestive secretion**

The digestive secretion period is divided into three phases which are cephalic, gastric and intestinal. The reason for this division is that of regulatory systems responsible for effecting secretion shifts as a function of location of meal and its effect on sensory inputs (Pandol, 2010).

The cephalic phase is the time before swallowing of food. This phase mediates secretion primarily from acinar cell. During this period several stimuli such as emotional state, taste of the meal and chewing are working. Their inputs are integrated in the central nervous system (dorsal vagal complex) and the vagus nerve transmits output to the exocrine pancreas. Anagnostides and colleagues reported that Sham feeding, such as chewing and spitting out of the food, in human stimulated pancreatic enzyme secretion with no increase in bicarbonate secretion (Anagnostides et al., 1984).

In gastric phase the secretion from pancreas occurs when the meal reaches stomach. In this phase gastric distension (Kreiss et al., 1996) acts as a major stimulant for pancreatic secretion. A partial digestion of the protein, lipid and carbohydrate in the meal by pepsin, lipase and amylase respectively create nutrient stimulants that activate secretion of digestive enzymes when delivered to intestine. This shows the inter relationship between the gastric phase and intestinal phase of the meal (Pandol, 2010).

Secretion from pancreas starts from the intestinal phase when chyme reaches small intestine from the stomach and it continues throughout the digestion period. This secretion is controlled and mediated by hormones and enteropancreatic vagovagal reflexes.

The secretion of the digestive enzymes in the intestinal phase takes place in a cascade mechanism which begins with the acid leaving stomach and entering duodenum. As a result secretin is released from the secretin containing S cells (Kontureck et al., 1969). The secretin interacts with its GPCRs on pancreatic ductal cells thereby stimulating volume of secretion and secretion of bicarbonate. The role of secretin in meal stimulated pancreatic fluid and bicarbonate secretion has been confirmed by showing that immune-neutralization of secretin by specific antisecretin antibody decreases their responses by as much as 80% (Song et al., 1999). Stimulants of enzyme secretion are predigested intraluminal fatty acids of more than eight carbon in length, monoglycerides of these fatty acids, peptides, amino acids and to a small extent glucose (Liddle et al., 1985; Go et al., 1970) which leads to release of CCK by the duodenum. This induces contraction of gall bladder and release of acetylcholine from intrapancreatic nerve fibers, which in turn stimulate enzyme secretion from pancreas.

To prevent the self digestion of the organ, most pancreatic enzymes are synthesized as zymogens and proenzymes which are inactive precursors (trypsinogen, chymotrypsinogen, proelastase etc) and additionally packaged in organelles (zymogen granules). Amylase is spontaneously active. Lipase has an intermediate status, being secreted as an active enzyme, but its lipolytic activity dependent on the activation of a cofactor (colipase). The exocrine enzymes are released from the acinar cells of the pancreas via a complex mechanism (the membrane of the zymogen granules fuses with the apical membrane of the acinar cells). The process of the activation of coenzymes begins in the duodenum with secretion of the enterokinase from the mucosa of the upper small intestine into the intestinal lumen. This results in the splitting off of a peptide (TAP) from trypsinogen which leads via a complex folding process to the formation of active trypsin. Trypsin is now in a
position to convey the remaining proenzymes into their active form (Mossner and Keim, 2011).

**Digestive enzymes from pancreas and their functions**

During metabolism, digestion is obligatory for absorption which occurs mainly via enzymatic hydrolysis. In this context, pancreatic enzymes particularly lipase, amylase, trypsin and chymotrypsin, play the critical role. The human pancreas has the largest potential for synthesis of protein and much of the capacity is directed towards the synthesis of the digestive enzymes that are secreted in the intestinal lumen.

Starch digesting enzyme amylase is synthesized and secreted by both pancreas and salivary gland but they differ in molecular weight and electrophoretic mobility (Meites and Rogols, 1971). However their enzyme activity is identical. Digestion begins in the mouth by salivary amylase which account for partial hydrolysis of starch and glycogen. The meal is then transported to stomach and small intestine where the salivary amylase still has some activity. The optimal enzyme activity is observed at neutral pH. The pH of pancreatic fluid is 7.0-8.7 and the pH of the duodenal fluid is 6.5-7.5. Additionally in the duodenum, there are Brunner gland secreting the mucus at pH 8.3-9.3 that neutralize the acidity of stomach fluid and protect the duodenum from secretion of the mucus at pH 8.3-9.3 that neutralize the acidity of stomach fluid and protect the duodenum from low pH of the content inflowing from the stomach (Ziarno, 2008). During a meal, the gastric pH can approach neutrality despite gastric acid secretion because of the buffering from molecules in the meal as well as alkaline secretion from the salivary glands and gastric mucosa. Salivary amylase can contribute up to 50% of starch and glycogen digestion while pancreatic amylase contributes to the remainder (Pandol, 2010). Both salivary and pancreatic amylases hydrolyse 1, 4-glycoside linkages of starch or other polymers. The hydrolysis products of amylase digestion are maltose, maltotriose and α-dextrins. The brush border enzymes complete the hydrolysis of the products of amylase digestion to glucose. The final product glucose is transported across the intestinal absorptive epithelial cell by Na⁺-coupled transporters (Kimmich, 1990; Wright et al, 2003).

Pancreas is the only main source of lipases. However there are also lingual and gastric lipases but their contribution to fat digestion is very insignificant. The most important fat digestive enzymes secreted by the pancreas are lipase and phospholipase.

Hydrolysis of triglyceride molecules are done by pancreatic lipase. As a result of hydrolysis two fatty acid molecules are released from carbon 1 and 3 and a monoglyceride with fatty acid esterified to glycerol is released from carbon 2 (Hofmann and Borgsriom, 1963). During enzyme hydrolysis of triglyceride, lipase binds to the olive/water interface of the said substrate. There are two important factors for optimum lipase activity and they are bile acids and colipase. Bile acids help in the formation of emulsion with triglyceride to enlarge the surface area for lipase to act on, and they form micelles with fatty acids and monoglyceride, which in turn remove their products from olive/water interface. Colipase forms a complex with lipase and bile salts. This ternary complex anchors lipase and allows it to act in a more hydrophilic environment on the hydrophobic surface of the oil droplet (Pandol, 2010).

Pancreas can produce two different types of proteases – the endopeptidases and exopeptidases. The exopeptidases can cleave peptide bonds releasing one amino acid at a time from the NH₂ or COOH terminal ends of a protein. The endopeptidases cleave peptide bonds internally in a protein at specific sites. For example exopeptidases are carboxypeptidases that cleave peptide bonds from COOH terminal of a protein and endopeptidases are chymotrypsin and trypsin. Trypsin cleavage is specific for the peptide bonds after arginine and lysine residues in the protein whereas chymotrypsin specifically cleaves peptide bonds after aromatic amino acids (Gorelick et al., 2003). All the stored and secreted proteases from panaceas are in their inactive proforms which are activated in the duodenum by trypsin.

During digestion of protein, the combined action of the pancreatic proteases and pepsin from the stomach result in the formation of oligopeptides and free amino acids. These oligopeptides are further digested by brush border enzymes on the luminal surface of the small intestine. Both free amino acids and oligopeptides are transported across the intestinal mucosa by a group of Na⁺ and H⁺ coupled transporters (Kilberg et al., 1993). These amino acids have greater effects on stimulating pancreatic secretion, inhibiting gastric juice emptying and regulating small bowel motility. Thus the specific pattern of protease actions leads to the physiological regulation of several organs in the gastrointestinal tract (Pandol, 2010).

**Pancreatic exocrine insufficiency**

Pancreas produces and secretes sufficient fluids containing enzymes, which help in break down of fat, carbohydrates and proteins. Pancreatic exocrine insufficiency occurs when the pancreas is not able to synthesize sufficient enzymes for proper digestion to take place. Pancreatic exocrine insufficiency is a major consequence of disease which resulted after the loss of pancreatic parenchyma (e.g. chronic pancreatitis, cystic fibrosis), obstruction of the main pancreatic duct (e.g. pancreatic and ampullary tumors), decreased pancreatic stimulation (e.g. celiac disease) or acid-mediated inactivation of pancreatic enzymes (e.g. Zollinger-Ellison syndrome). In addition, gastrointestinal and pancreatic surgical reactions (e.g. gastrectomy or duodenopancreatectomy) are frequent cases of pancreatic exocrine insufficiency due to post cibal asynchrony, decreased pancreatic stimulation and loss of pancreatic parenchyma. The majority of the patients with chronic pancreatitis eventually develop pancreatic exocrine insufficiency depending on the etiology of the disease (Dominguez-Munoz, 2011). Because of large residual capacity of pancreas, exocrine insufficiency becomes clinically apparent only when 90% of the function is lost (Lankisch et al., 1986; Layer et al., 1986). Post operative...
Pancreatic exocrine insufficiency is often observed in 65 – 80% of the patients with chronic pancreatitis (Riediger et al., 2007). In patients with pancreatic cancer exocrine insufficiency is found in 68 to 92% before surgery and 80% after surgery (Kato et al., 1993).

As pancreatic lipase is mainly responsible for fat digestion in the human digestive system, exocrine insufficiency leads to malabsorption which causes steatorrhea, weight loss and malnutrition (Pasquale et al., 1996; Rivers and Hassan 1975; Roberts, 1989). It is associated with deficiencies of the fat soluble vitamins (vitamin A, D, E & K), magnesium, calcium and essential fatty acids and amino acids (Dutta et al., 1982; Kalivianakis et al., 1999; Lankisch et al., 1986a).

**Diagnosing of pancreatic exocrine insufficiency**

Many methods are reported (Dominguez-Munoz, 2011) for the functional evaluation of exocrine pancreas. But it is often difficult to detect pancreatic exocrine insufficiency in routine clinical practice because the patients are usually asymptomatic in the early stages of pancreatic exocrine insufficiency (Nakajima et al., 2012). However it is always recommended to detect the disease clinically as early as possible.

Different methods such as secretin-pancreozymin test or endoscopy (Hammer, 2010; Chowdhury and Forssmark, 2003), quantification of fat absorption and 13C –mixed triglyceride breath test (Dominguez-Munoz, 2011) are followed for the clinical detection of the pancreatic exocrine insufficiency. Several non-invasive and inexpensive tests, such as measurement of fecal elastase-1 concentrations, are also useful to determine reduced pancreatic secretion in patients with different pancreatic diseases (Leeds et al., 2011; Chowdhury and Forssmark, 2003).

**Treatment of pancreatic exocrine insufficiency**

Pancreatic exocrine insufficiency is often observed in patients with different types of pancreatic diseases. These diseases often resulted in malnutrition, weight loss and steatorrhea which together increase the risk of morbidity and mortality (Nakajima et al., 2012). Therefore nutritional interventions such as low fat diets and pancreatic enzyme replacement therapy are needed to improve clinical symptoms and to address the pathophysiology of the disease.

Classically, the initial approach to patients with pancreatic exocrine insufficiency is to restrict fat intake in an attempt to reduce steatorrhea. A diet containing less than 20g fat daily is thus recommended in this context. It is also advised for frequent low volume meals and to avoid food which is difficult to digest (Dominguez-Munoz, 2011).

Pancreatic enzyme replacement therapy is the mainstay of the treatment for pancreatic exocrine insufficiency. The objective is to deliver sufficient enzyme activity into the duodenal lumen simultaneously with the meal in order to restore normal digestion which aid absorption.

The relationship between dose of pancreatic enzymes required and the occurrence of malabsorption and maldigestion is not linear. Therefore, patients should start on lower recommended dose of pancreatic enzymes, which should be increased as and when required. The pancreatic enzyme formulations should be taken with the meal to ensure adequate mixing with the chyme (Dominguez-Munoz et al., 2005). Clinically measured parameters example, weight gain, improvement of diarrhea, reduction of steatorrhea and improvement of abdominal pain are the signs of treatment success. Pancreatin therapy is associated minor side effects (Table 1).

**TABLE 1**

List of adverse effects of pancreatic enzyme therapy.

<table>
<thead>
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<th>Effect</th>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Hypersensitivity of porcine enzymes (protein)</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Inflammatory colonic stenoses</td>
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<td>Soreness in mouth</td>
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**Commercial available pancreatic enzyme products**

Pancreatic enzyme preparations in the form of pH sensitive enteric-coated minimicrospheres are currently available in the market. Although enteric – coated tablets and enteric coated granules are available in the market, these formulations are developed to protect the enzyme activity while passing through the low intraluminal pH and to avoid the problem of pyloric retention. These minimicrospheres are dispersed more rapidly in the chyme.

The therapeutic requirements for a pancreatic preparation are that it must have high lipase activity, protect the lipase from being destroyed by gastric acid, mix with the chyme and leave the stomach with it and also rapid release of pancreatin out of enteric coating into the duodenum. The other factors which are important for the effectiveness of an enzyme preparation are particle size and the time taken for the release of enzymes from the duodenum (Mossner and Keim, 2011). The most suitable particle size is reported to be a diameter of ≤ 2 mm, as these particles can exit stomach at the same time as solid food (Kuhnelt et al., 1991). Stead and colleagues reported that compared to standard tablets, microsphere capsules of pancreatin produce clear subjective and objective evidence of reduction in steatorrhea, including 44% reduction in fecal fat excretion (Stead et al, 1987). A randomized, double-blind placebo controlled trial in chronic pancreatitis patients has shown the significant therapeutic efficacy of these minimicrospheres of pancreatin in reducing fat excretion, decreasing stool frequency and improving stool consistency (Saffidi et al., 2006).

**Dosage**

Formulations used for pancreatin enzyme therapy are orally administered capsules which contain delayed release pancreatin derived from porcine. Dosage of
pancreatic enzyme preparation is individually tailored. These capsules are always prescribed to be taken with food. When swallowing of capsules is difficult the capsules may be opened and the contents added to a small amount of low acidic soft food with a pH less than 5.5 such as apple sauce, pudding, mashed or pureed bananas or carrots at room temperature.

Dosage should be individualized by patients according to the degree of malabsorption and the fat content of the meal. The required dose for a meal (breakfast, lunch or dinner) ranges from about 20,000 to 75,000 Ph. Eur. Units of lipase and for in between snacks about 5000-25,000 Ph. Eur. Units of lipase. The usual initial starting dose for pancreatic enzyme replacement therapy is 10,000-25,000 Ph. Eur. Units of Lipase per main meal (Pancreatic enzymes in the WHO Model List of Essential Medicines, 2008). However patients may need higher doses to minimize steatorrhea and maintain good nutritional status. Customary clinical practice suggests that at least 20,000-50,000 Ph. Eur. Units of lipase should be given with the meal and should be doubled if required for adequate lipolytic digestion (Layer et al., 2001). However it is always recommended that dosage of pancreatic enzyme preparations should be adjusted in accordance to the need of the individual patient.

Conclusions

The patients with symptoms of pancreatic exocrine insufficiency, lipid malabsorption is considered to be clinically most significant. Thus pancreatic enzyme replacement therapy remains the mainstay treatment for the pancreatic exocrine insufficiency. To make the therapy more effective, administration of bacterial lipase from Burkholderia plantarii might have a good potential. This bacterial lipase has a high specific activity, is resistant to gastric acid and proteolytic enzyme, is not inhibited by bile acids and is superior compared with porcine pancreatin in correcting fat malabsorption (Raimondo and DiMaggio, 1994; Suzuki et al., 1997). Beside this, basic and clinical studies need to address the identification of genetic factors predisposing individuals to pancreatic insufficiency. However the human pancreatic lipase gene has been successfully transfected and expressed in vitro and in vivo. Significant production of human lipase was observed under these considerations (Kuhel et al., 2000; Maeda et al., 1994). Further more application of bioengineered acid resistant human gastric of Essential Medicines, 2008). However patients may need higher doses to minimize steatorrhea and maintain good nutritional status. Customary clinical practice suggests that at least 20,000-50,000 Ph. Eur. Units of lipase should be given with the meal and should be doubled if required for adequate lipolytic digestion (Layer et al., 2001). However it is always recommended that dosage of pancreatic enzyme preparations should be adjusted in accordance to the need of the individual patient.

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