14 Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain

Gyanprakash A. Ketwaroo and David Y. Graham

Abstract

We describe the rational use of enteric coated and unprotected replacement pancreatic enzymes for treatment of malabsorption due to pancreatic insufficiency and for pancreatic pain. Enteric coated formulations mix poorly with food allowing separation of enzymes and nutrients when emptying from the stomach. The site of dissolution of the enteric coating in the intestine is also unpredictable and enzymes may not be released until the distal intestine. Together, these barriers result in the lack of dose-response such that the strategy of increasing the dosage following a suboptimal effect is often ineffective. The ability to maintain the intragastric pH ≥4 with the combination of proton pump inhibitors and antacids suggests that it should be possible to reliably obtain a good response with uncoated enzymes. We also discuss the recognition, treatment and prevention of nutritional deficiencies associated with pancreatic insufficiency and recommend a test and treat strategy to identify and resolve nutritional deficits. Finally, we focus on mechanisms causing pain that may be amenable to therapy with pancreatic enzymes. Pain due to malabsorbed digestive contents can be prevented by successful therapy of malabsorption. Feedback inhibition of endogenous pancreatic secretion can prevent pain associated with pancreatic secretion but requires use of non-enteric coated formulations.

Keywords

Pancreatic enzymes · Pancreatic insufficiency · Chronic pancreatitis

Abbreviations

CCK	Cholecystokinin
CFA	Coefficient of fat absorption
FDA	Food and Drug Administration
INR	International normalized ratio
RBP	Retinol binding protein

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14.1 Introduction

Most food is ingested in the form of macromolecules that can only be absorbed after being reduced to smaller molecules. The pancreas is the primary source of enzymes involved in the digestion of carbohydrates, proteins, and fats. In addition to supplying enzymes, the pancreas produces bicarbonate to neutralize the gastric acid and provide the proper milieu for the enzymes to function. The absorptive and digestive capacity of the intestinal tract is large and has great redundancy such that the majority of the small intestine must be bypassed for successful bariatric surgery.

Lipid digestion and absorption is the most complicated requiring four distinct steps. The process begins by synthesis of lipases by pancreatic acinar cells which are then secreted through the pancreatic ducts into the duodenum in response to food entering the duodenum. The gastric contents entering the duodenum are acidic and the acidity must be neutralized by secretion of duodenal and pancreatic bicarbonate in order for the enzymes and bile acids to function properly. Lipase is irreversible inactivated if the pH falls to pH 4 or below. When there is insufficient duodenal pancreatic enzyme activity, exocrine pancreatic insufficiency occurs (Table 14.1). This condition can occur due to causes directly related to the pancreas such as loss of pancreatic acini, blockage of the pancreatic ducts preventing secretion of enzymes, or acidic duodenal contents which inactivate pancreatic lipase. Other causes are related to failure to stimulate pancreatic secretion and inability of the secreted enzymes to properly mix with duodenal contents (Table 14.1) (Singh et al. 2017).

Table 14.1 Causes of exocrine pancreatic insufficiency (insufficiency (insufficient intraluminal pancreatic enzyme activity)

Loss of pancreatic acini
Pancreatic inflammation, pancreatic resection, cystic fibrosis, pancreatic malignancy, cystic fibrosis,
Inability of secreted enzymes to enter the duodenum
Pancreatic ductular obstruction (fibrosis, stricture, stones, malignancy)
Altered anatomy (e.g., Roux-en-y gastric bypass
Acidic duodenal pH
Zollinger Ellison syndrome, defective pancreatic bicarbonate secretion
Insufficient stimulation of enzyme secretion (celiac disease)

14.2 Exocrine Pancreatic Insufficiency

14.2.1 Diagnosis

The diagnosis of pancreatic insufficiency requiring adjuvant enzyme replacement is typically based on clinical suspicion followed by laboratory confirmation or by confirmation of improvement of weight and nutritional deficiencies following enzyme replacement therapy. Fat malabsorption (steatorrhea) clinically presents as weight loss with large, foul smelling, pale, pasty stools. The stools may appear greasy and an oily sheen reflecting undigested triglycerides may be visible on the water in the toilet bowl. The presence of watery diarrhea and floating stools are often mentioned by students as important diagnostic features, but watery diarrhea is an uncommon presentation and stools float because of trapped air rather than the presence of fat in stools.

Pancreatic insufficiency can be confirmed by pancreatic function testing directly via the secretin pancreatic function test where duodenal juice is collected endoscopically or using a special "Dreiling" tube. The pancreatic fluid bicarbonate concentration is then measured, with normal being >80 mEq/L (Diamond et al. 1940; Dreiling and Hollander 1948; Ketwaroo et al. 2013; Pelley et al. 2012). This approach is highly sensitive and is able to stratify pancreatic dysfunction as mild, moderate or severe. However, the test is invasive, expensive and labor intensive (Diamond et al. 1940). Non-invasive tests are available and the gold standard non-invasive test is quantification of fat malabsorption by measuring 72-h fecal fat excretion. An abnormal result is excretion of more than 7% of ingested fat and is best expressed as a coefficient of fat absorption (e.g., >7 g while receiving a 100 g fat diet). Fecal fat measurement is often not offered because it requires collecting and handling of stools. This problem continues despite improved methodology that obviate the

need for homogenization of stools, such as measuring fat content using near infrared spectrometry (Benini et al. 1989). Alternate indirect methods of assessing pancreatic exocrine function include measuring fecal concentrations of pancreatic enzymes, such as elastase 1 or chymotrypsin. Where available, breath tests are preferred. This approach assesses fat absorption directly follow administration of labeled triglycerides such as the carbon 13 triglyceride breath test (Afghani et al. 2014; Dominguez-Munoz et al. 2007). The most widely available test is measuring fecal elastase I.

14.2.2 Fecal Elastase 1

Elastase 1 is an enzyme produced by the pancreas. It is resistant to digestion and passes largely intact through the intestinal tract where its concentration is measured in the stool. The most common test format is as an enzyme-linked immunosorbent assay which uses a monoclonal antibody specific to human elastase I (Stein et al. 1996; Struyvenberg et al. 2017). The test result is therefore not influenced by the presence of the antigenically distinct exogenous porcine pancreatic enzymes so that enzyme therapy need not be withheld. The main caveat regarding interpretation is that the test is only accurate when done using formed stools (Struyvenberg et al. 2017). The cut-off value for a normal result is >200 μg/g feces. Values between 100 and 200 μg/g feces are considered indeterminate and values below 100 μg/g feces are highly suggestive of pancreatic insufficiency. However, as with any test, interpretation depends on the pretest probability and, in our experience, fecal elastase I testing is often ordered in the evaluation of patients with diarrhea where false positive test results are common. A recent review and meta-analysis of the role of fecal elastase testing in the diagnosis of exocrine pancreatic insufficiency concluded that a normal value was highly indicative of absence of pancreatic insufficiency (pooled sensitivity of 0.96 and specificity of 0.88). The false negative rate was 1.1% and the false positive rate, 11%. It followed that in high pretest probability conditions, only about 10% of cases of chronic exocrine insufficiency would be false negatives (Vanga et al. 2018).

14.2.3 Treatment of Exocrine Insufficiency

Pancreatic replacement enzymes have been available clinically since at least the late 1800s (Engesser 1879) and the most common source of pancreatic enzymes remains desiccated hog pancreas. Bovine pancreas preparations are also available but are used much less frequently and microbial lipases are just beginning to be used (Heubi et al. 2016; Lowe and Whitcomb 2015). It is expected that use of microbial derived enzymes will likely grow. Commercial products are described clinically in terms of lipase content (e.g., 20,000 USP lipase units).

Although it seems obvious that replacing the missing enzymes should be a successful strategy there are many myths (Table 14.2) and numerous impediments preventing normalization of digestion and correction of pancreatic exocrine insufficiency. Long ago, our forefathers discovered that simply feeding pancreatic enzymes did not reliably produce the desired effect and that gastric acid rapidly inactivated ingested pancreatic lipase (Chase 1905). Various methods have been attempted to overcome this acid barrier including administration of enzymes with antacids with or without anti-secretory agents and protecting the enzymes with enteric coating. As discussed below, none has proved reliably successful. Here, we discuss the limitations of replacement therapy as well as the weaknesses and misconceptions related to current practices. Current guidelines

Table 14.2 Myths related to treatment of exocrine pancreatic insufficiency

60,000 units of lipase should be administered with each meal
Increasing the dose (i.e., number of capsules or lipase units) reliably increases the effect
Increasing the enzyme dosage is a safe and effective strategy
Non-enteric coated preparations are almost always ineffective and should not be used
Proton pump co-therapy (e.g., 20 mg omeprazole) reliably improves treatment outcome
Enteric coated preparations are useful for treatment of pancreatic pain
The most reliably way to confirm therapy is effective is by symptom response

often seem to represent urban myths rather than recommendations based on scientifically sound principles. The treatment outcome is assessed based on the ability to normalize absorption of fats, which requires coordination of lipid hydrolysis, solubilization of the digestive products by bile, and absorption by the small intestine.

14.3 Pancreatic Enzymes

14.3.1 Dosing of Pancreatic Enzymes

The FDA approved package insert for a typical commercial product (e.g., Creon®) states that "the initial starting dose [of pancreatic enzymes] and increases in the dose per meal should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet" (https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020725s000lbl.pdf). They refer to a clinical trial where patients received 72,000 lipase units per meal while consuming at least 100 g of fat per day and cite the Cystic Fibrosis Foundation Consensus Conferences Guidelines of 500 lipase units/kg of body weight per meal as the lowest starting dose (Stallings et al. 2008). They further note that "there is great inter-individual variation in response to enzymes; thus, a range of doses is recommended" and that "if doses exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted". Doses greater than 2500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution" and that "patients currently receiving higher doses than 6000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range".

In contrast, Forsmark in Sleisenger and Fordtran's Gastrointestinal and Liver disease textbook suggests that 90,000 USP units of lipase are needed with each meal (Forsmark 2016). Broad recommendations such as therapy being individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet do not identify which of the variables is best or whether all three are equivalent. Because clinicians rarely have access to the patients' degree of steatorrhea, the recommendation forces clinicians to rely on symptoms and fat content of the diet. However, no guidance is provided to advise the patient what characteristics they should use to judge the fat content of the diet or what adjustments they should make. In actual practice, following the advice of the package insert or the textbook will not reliably achieve the goal of resolving malabsorption or the nutritional consequences of pancreatic insufficiency.

Here, we attempt to provide a practical approach to assist patients and clinicians. First, we address the evidence regarding the quantity of lipase required to correct steatorrhea. Recommendations are given in terms of amount of lipase but this is confusing as lipase is described in different units in different countries. In the United States, FDA-approved products are described in USP lipase units (1 IU = 3 USP units). We will describe results of different studies in USP units. Current FDA-approved pancreatic enzyme products range from 3000 USP lipase units to 36,000 USP units per pill (Table 14.3). Outside of the United States a wide variety of preparations are available (Ianiro et al. 2016)

Under normal physiologic circumstances post prandial lipase secretion has been estimated at 9000–18,000 USP units/min (Keller et al. 1997; Keller and Layer 2005) totalling between 120,000 and 2,196,000 USP units in the 3 h post prandial period (DiMagno et al. 1977). Based on intubation studies in humans it has also been suggested that only 5–10% of normal pancreatic output is required for normal fat absorption (DiMagno et al. 1973; Kalser et al. 1968; Regan et al. 1979).

For steatorrhea to be abolished following oral administration of pancreatic enzymes requirements include that (a) the enzyme remain active and (b) mix and (c) empty with the meal which is (d) coordinated with the entry of bile into the duodenum and normal small intestinal motility and absorptive function. Studies have shown that administration of approximately 30,000 USP lipase units/meal of unprotected pancreatic enzymes can eliminate steatorrhea in those with absent or low acid secretion (Fig. 14.1) (Graham

Table 14.3 FDA approved pancreatic enzyme preparations

Drug	Lipase (USP units)	Preparation	Diameter (mm)
CREON®			
Creon 3000	3000	Capsule with enteric coated minimicrospheres	0.71–1.6
Creon 6000	6000	Capsule with enteric coated minimicrospheres	0.71–1.6
Creon 12000	12,000	Capsule with enteric coated minimicrospheres	0.71–1.6
Creon 24000	24,000	Capsule with enteric coated minimicrospheres	0.71–1.6
Creon 36000	36,000	Capsule with enteric coated minimicrospheres	0.71–1.6
Pancreaze®			
Pancreaze 4200	4200	Capsule with enteric coated microtablets	2
Pancreaze 10500	10,500	Capsule with enteric coated microtablets	2
Pancreaze 16800	16,800	Capsule with enteric coated microtablets	2
Pancreaze 21000	21,000	Capsule with enteric coated microtablets	2
Zenpep®			
Zenpep 3000	3000	Capsule with enteric coated beads	1.8–1.9
Zenpep 5000	5000	Capsule with enteric coated beads	1.8–1.9
Zenpep 10000	10,000	Capsule with enteric coated beads	2.2–2.5
Zenpep 15000	15,000	Capsule with enteric coated beads	2.2–2.5
Zenpep 20000	20,000	Capsule with enteric coated beads	2.2–2.5
Zenpep 25000	25,000	Capsule with enteric coated beads	2.2–2.5
Ultresa®			
Ultresa 13800	13,800	Capsule with enteric coated minitablet	2
Ultresa 20700	20,700	Capsule with enteric coated minitablet	2
Ultresa 23000	23,000	Capsule with enteric coated minitablet	2
Pertyze®			
Pertyze 8000	8000	Capsule with bicarbonate buffered enteric coated microsphere	0.8–2.2
Pertyze 16000	16,000	Capsule with bicarbonate buffered enteric coated microsphere	0.8–2.2
Viokace®			
Viokace 10440	10,440	Non-enteric coated	
Viokace 20800	20,880	Non-enteric coated	

pH at or above which enzyme is designed to release most of the enzyme based on the package insert

1977). The duration of the postprandial gastric pH ~4 and the average duodenal pH was also shown to correlate with the percentage reduction in steatorrhea (i.e., the longer the gastric pH remained ~4, the higher the average duodenal pH, and the more reduction in steatorrhea achieved). Another study also showed complete resolution of steatorrhea in two of six patients with 18,000 USP lipase units/meal of enteric-coated microspheres given throughout the meal (Fig. 14.2) (Graham 1979). One can therefore conclude that in adults with pancreatic steatorrhea between 18,000 and 30,000 USP units of lipase per meal is sufficient to eliminate steatorrhea. The difficulty is how to "deliver a sufficient amount of active lipase at the right place, i.e., duodenum and proximal jejunum, and at the right time, i.e., in parallel with gastric emptying of nutrients," (Table 14.3) (Trang et al. 2014).

14.3.2 Barriers to Delivery of Sufficient Active Lipase to the Duodenum and Proximal Jejunum in Parallel with Gastric Emptying of Nutrients

There are remarkably few data available showing how to reliably achieve resolution of malabsorption with orally administered pancreatic enzymes. The normal digestive process provides integration of gastric emptying with pancreatobiliary

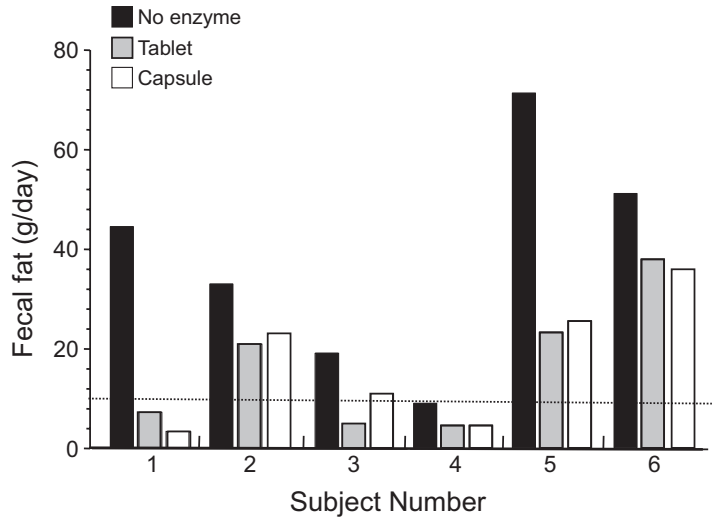

Fig. 14.1 Comparison of baseline and therapy with enzymes formulated as tablets or capsules in adults with exocrine pancreatic insufficiency. Approximately 30,000 USP units of lipase were given with meals. Correction of steatorrhea correlated with time the gastric pH was 4 or greater. (Adapted from Graham 1977. Copyright © 1977 Massachusetts Medical Society)

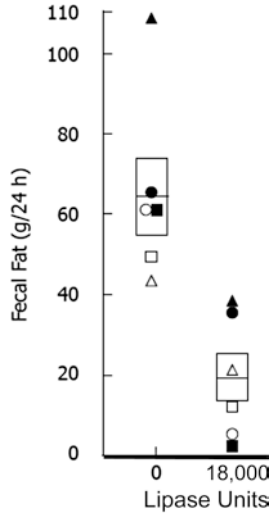

Fig. 14.2 Effect of increasing the enzyme dosage on fecal fat excretion while receiving a 100 g fat diet. Enzymes were given three times per day with meals providing 18,000 USP lipase units as enteric coated microspheres (i.e., three microsphere capsules with each meal). Each rectangle encloses the mean ± the standard deviation of the mean. The normal fecal fat is <6 g/24 h. (Adapted from Graham 1979)

secretion to provide ideal conditions in terms of pH and enzyme concentration to promote digestion and absorption of the nutritional elements despite marked differences in the composition and quantity of meals.

When pancreatic enzymes are administered orally they can either mix with or separate from the meal. They can also either survive or be destroyed by acid-pepsin. By 1905 it was noted that pancreatin "was rendered inert" by gastric juice (Chase 1905) and that enteric coating of the enzymes either failed to protect the enzymes or failed to dissolve rapidly enough "to allow the pancreatin to be of any service in digestion" (Chase 1905). The stomach is only one of the barriers to successful therapy as altered gastrointestinal motility and reduced pancreatic bicarbonate secretion also result in unpredictable destruction, transit or dissolution of administered enzymes (DiMagno et al. 1977; Layer et al. 1986). One common strategy has been to administer large quantities of pancreatic enzymes in an attempt to overpower the gastric barrier. Experience has shown that this rarely restores normal fat absorption (Beazell et al. 1941; DiMagno et al. 1977; Harris et al. 1955; Jordan and Grossman 1959; Littman and Hanscom 1969). The option of using enteric coating to protect the enzymes has also had limited success as it has been plagued both by separation of the enteric coated enzymes from the meal and the fact that the proximal intestine often remains acidic which delays dissolution of the coating and release of the enzymes to the distal small intestine and colon (Aloulou et al. 2008; Delchier et al. 1991).

14.3.3 Gastric Emptying Barrier

Gastric emptying is normally highly regulated by receptors in the duodenum that respond to the pH, osmolarity, and nutrient content of the contents entering from the stomach (Hunt 1983; Hunt and Knox 1968; Smith et al. 1984). The stomach acts as a reservoir which acidifies, grinds, and sieves the gastric contents such that small particles (e.g., <1 mm) suspended in liquid are the major form of the meal that exits into the duodenum (Meyer 1980; Meyer et al. 1988; Meyer and Lake 1997). The addition of nutrients to the stomach also results in robust acid secretion such that the pH is typically above four for only a short period after eating. The lack of pancreatic bicarbonate and enzymes results in more rapid emptying and inability of the duodenum to control the pH and maintain the ideal milieu for digestion (DiMagno et al. 1977; Layer et al. 1986).

14.3.4 Overcoming the pH Barrier

As noted previously, lipase is irreversibly inactivated at pH 4 or below. The gastric pH barrier often extends into the duodenum. Attempts to overcome the pH barrier include enteric coating of enzymes and/or the use of antacids or antisecretory drugs to increase the intragastric/duodenal pH.

14.3.5 Coating of Enzymes

Most pancreatic enzyme preparations available in the United States are packaged as enteric coated microspheres. The only exception is Viokace®. Pertyze® is enteric coated but also contains a small amount of bicarbonate in the outer layer. The amount of bicarbonate present is too small to be functionally important. While the enteric coated enzyme products are available in different dosages (Table 14.3), the amount of lipase is increased by packaging identical microspheres in larger capsules which containing more beads.

In 2004 the FDA mandated that all pancreatic enzymes be reformulated to meet new specifications including minimum and maximum amounts of enzyme and dissolution characteristics under defined conditions (Trang et al. 2014). The regulation was prompted by the wide variability of products including generic enteric coated products that often failed to protect the enzymes in transit through the stomach (Kuhn et al. 2007). The bar for clinical approval was very low as they only had to prove to be superior to placebo (Trang et al. 2014). The outcome was a reduced number of products and a large increase in price. Most FDA- mandated post-approval studies to better understand why the results were relatively poor have been completed but the results have not been revealed (Trang et al. 2014). Since 2010 only the newly approved products are available in the U.S., although over-the-counter products remain available at health food stores. These are typically not enteric coated and lipase activity is measured in different units such that interpretation required translation (Table 14.4.) (Scharpé et al. 1997).

Currently available enteric coated microbead enzymes are effective in protecting the acid-sensitive lipases from inactivation in the stomach and have proven more effective than placebo in reducing steatorrhea (Trang et al. 2014). However, they frequently fail to entirely correct malabsorption. Importantly, the strategy of administration of more microbeads (i.e., increasing the dosage) generally fails to provide a further reduction in steatorrhea (i.e., there is absence of a dose response) (da la Iglesia-García et al. 2017; Trang et al. 2014). The lack of a dose

Table 14.4 Conversion of relative potency of enzymes based on different units of measurement

Amylase: 1 Ph.Eur. Unit = 1 BP Unit = 1 FIP Unit ~ 4.15 USP Units
Lipase: 1 Ph.Eur. Unit = 1 BP Unit = 1 FIP Unit ~ 1 USP Unit = 1/3 IU
Protease: 1 Ph.Eur. Unit = 1 BP Unit = 1 FIP Unit ~ 62.5 USP Units

Ph.Eur European Pharmacopoeia, *BP* British Pharmacopoeia, *FIP* International Pharmaceutical Federation, *USP* United States Pharmacopoeia, *IU* International Units

response prevents dose escalation as an effective treatment strategy to achieve the desired clinical response (Trang et al. 2014). Overall, many patients do well by relying only on enteric coated microbeads despite only partial relief of steatorrhea but a proportion continues to experience nutritional deficiencies (da la Iglesia-García et al. 2017; Dominguez-Munoz et al. 2007; Lindkvist et al. 2015; Trang et al. 2014).

The lack of dose-response and the relatively poor treatment response is often related to the fact that enteric coated microspheres rapidly separate from bulk food/nutrients. They thus are neither uniformly distributed within the meal nor reliably emptied along with the nutrients (Trang et al.). This results in dietary fat being emptied into the duodenum without the accompanying lipase needed for lipid digestion. The enteric coating used is slow to dissolve even in highly buffered alkaline media in vitro (Trang et al.). Impaired bicarbonate secretion in the duodenum of patients with pancreatic insufficiency produces an acid milieu such that the microbeads may not dissolve and release the contents until in the distal jejunum, ileum, or colon (DiMagno et al. 1977; Layer et al. 1986; Trang et al. 2014). Attempts have been made to compensate for this incoordination by giving some enzymes immediately before, throughout, or after the meal (da la Iglesia-García et al. 2017; Dominguez-Munoz et al. 2005; Trang et al. 2014). The effects of this strategy have been studied in a number of FDA mandated studies. The fact that as of April 2018 the results have not been published or reported suggests that the issues with incoordination of the process have not been solved (e.g., Pancrease https://clinicaltrials.gov/ct2/show/study/NCT00676702?term=NCT00676702rank=1 –Completed with 13 participants but no results posted (NCT00676702). Pancrecarb https://clinicaltrials.gov/ct2/show/NCT00744250?term=NCT00744250rank=1 – And https://clinicaltrials.gov/ct2/show/NCT00749099?term=NCT00749099rank=1. Both terminated as no longer required by FDA, 3 enrolled. NCT00744250; 11 enrolled NCT00749099. Viokase – https://clinicaltrials.gov/ct2/show/NCT00559052?term=NCT00559052rank=1 completed with 22 participants, no results posted. NCT00559052).

Although increasing amounts of enzyme microbeads often fails to produce a meaningful reduction in steatorrhea, there is also a risk that dumping a high concentration of pancreatic enzymes or, more importantly, of the highly acidic enteric coating into the colon can result in development of colonic strictures. This is particularly a problem in children (Bakowski and Prescott 1997; Franzen et al. 2008; Gaia et al. 2001; Prescott and Bakowski 1999; Prieto et al. 2009; van Velzen et al. 1996). Colonic strictures were initially attributed to the high concentration of pancreatic enzymes but as other drugs using the same coating have caused colonic stricture the evidence suggests that the highly acid coating may actually be the agent responsible for colonic damage (Prescott and Bakowski 1999; van Ball et al. 1996).

14.3.6 Use of Adjuvant Antacids and Anti-secretory Agents

The recognition that unprotected pancreatic enzymes could be inactivated during transit through the stomach led early investigators to try antacids to prevent enzyme inactivation. The early studies used arbitrary amounts of antacids but showed that co-administration of sodium bicarbonate or aluminum hydroxide with enzymes was partially effective (Durie et al. 1980; Gow et al. 1981; Kalser et al. 1968; Kattwinkel et al. 1972; Veeger et al. 1962; Weber et al. 1976). Fordtran et al., provided a more scientific basis for effective use of antacids for healing of peptic ulcers disease based on timing and dosages of antacid administration designed to enhance and extend the buffering capacity of meals (Fordtran et al. 1973). However, the goal of antacids to heal peptic ulcers differs from what is required of antacids when used as adjuvants to protect pancreatic enzymes. The critical difference between the two objectives is the need to prevent the intragastric pH from falling to pH 4 or below while the enzymes are in the stomach.

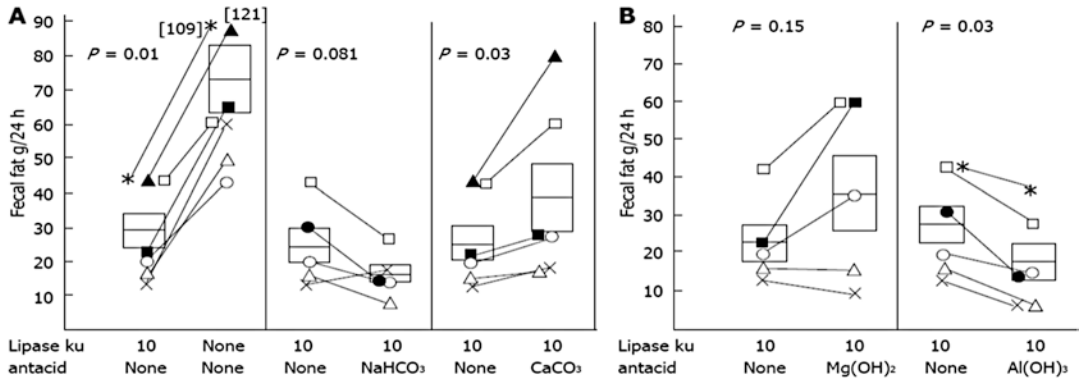

Fig. 14.3 Effect of antacids and enzymes on the effectiveness of 30,000 USP units of lipase per meal for the treatment of pancreatic steatorrhea. Each symbol represents a different patient. Box represents the mean ±SEM for the group. Number in [ ] = weight of stool. Sodium bicarbonate, magnesium aluminum hydroxide, aluminum hydroxide, or calcium carbonate were administered at the beginning and the termination of each meal. (Adapted from Graham 1982)

In a randomized study, we compared the effectiveness of sodium bicarbonate (1.3 g or 12 mEq), aluminum hydroxide (30 mL or 57 mEq), magnesium-aluminum hydroxide 30 mL or 72 mEq), or calcium carbonate (1 g or 21 mEq) administered before and immediately after each meal in improving steatorrhea in subjects receiving a low dose of lipase per meal while receiving 100 g fat/day (Graham 1982). The dose of lipase was expected to, on average, reduce steatorrhea by 50%. Those receiving adjuvant therapy with sodium bicarbonate or aluminum hydroxide experienced a reduction in steatorrhea (Fig. 14.3) (Graham 1982). Although all of the antacids lengthened the time the intragastric pH was >6 and increased duodenal pH and increased lipolysis, adjuvant therapy with calcium carbonate or magnesium-aluminum hydroxide resulted in worsening of steatorrhea and partially negated the benefits of enzyme therapy (Fig. 14.3) (Graham 1982; Graham and Sackman 1982). It was shown that the antacids did not impair lipase function and while calcium and magnesium-containing antacid therapy improved lipolysis, the released fatty acids combined with calcium or magnesium to produce calcium or magnesium soaps which were poorly absorbed (Graham 1982; Graham and Sackman 1982, 1983) introducing a new barrier to absorption.

H_2-receptor antagonists are generally incapable of maintaining the intragastric pH >4 which is required to prevent lipase inactivation (Graham 1982; Hunt et al. 1995; Jones et al. 1987). In contrast, while once daily administration of a proton pump inhibitor is able to increase the intragastric pH to ≥4, the duration is typically short (Bell et al. 1992; Graham and Tansel 2018). Studies with omeprazole and enteric coated pancreatic enzymes in cystic fibrosis patients with persistent steatorrhea despite use of enteric coated enzymes, confirmed that enzyme dose escalation failed to reduce steatorrhea whereas the strategy of increasing the enzymes along with adjuvant omeprazole was beneficial (Fig. 14.4) (Heijerman et al. 1991). Most subsequent studies with currently available enteric coated enzyme preparations have not demonstrated consistent benefits with adjuvant proton pump inhibitor therapy with the possible exception of those whose poor response was due to high gastric acid secretion (Bruno et al. 1994; Dominguez-Munoz et al. 2005; Marotta et al. 1989; Sander-Struckmeier et al. 2013).

Because of the general inability of adjuvant proton pump inhibitor therapy, as currently prescribed, to provide meaningful benefits this approach is not recommended for all patients (Dominguez-Munoz 2007). This admonition should now be reconsidered based on better understanding of how to use proton pump inhibitors to maintain the intragastric pH ≥4 (Graham and Tansel 2018).

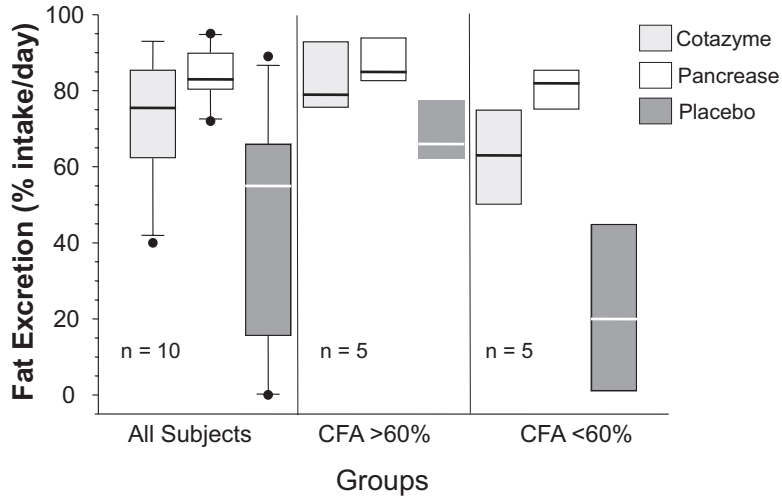

Fig. 14.4 Randomized cross-over comparison of similar amounts of lipase administered as unprotected enzyme capsules (Cotazyme®) or enteric-coated microspheres (Pancrease®) on coefficient of fat absorption (CFA) in cystic fibrosis patients with pancreatic insufficiency. Although the enteric coated preparation was better in those with the greatest degree of malabsorption (CFA <60%), neither formulation resulted in resolution of steatorrhea. (From Trang et al. 2014, with permission)

14.3.7 Combined Proton Pump Inhibitor and Antacid Adjuvant Therapy

The comparative effectiveness of different proton pump inhibitors in maintaining the intragastric pH above a desired pH (here, pH >4) for the entire 24 h day (pH4time) can be expressed in terms of omeprazole equivalents (Graham and Tansel 2018; Kirchheiner et al. 2009). Studies of pH4time are typically done after 5 days of therapy to ensure that steady state has been achieved. When different PPIs are given once daily the median pH 4 time increases linearly from approximately 30% (~7 h) following administration of about 2.5 mg omeprazole equivalents (equal to 10 mg of pantoprazole) to approximately 60% (~14 h) with about 70 mg omeprazole equivalents (equal to 40 mg of esomeprazole or rabeprazole). Most published studies of adjuvant proton pump therapy with pancreatic enzymes have used 20 mg of omeprazole once daily which produces a median pH 4 time of approximately 45% (10.8 h) (Fig. 14.5) (Graham and Tansel 2018). With 20 mg of omeprazole given twice daily the pH 4 time is approximately 70% (~17 h) and increases linearly to approximately 85% (~20 h)

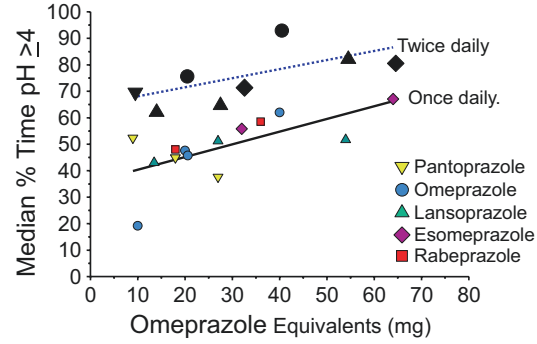

Fig. 14.5 Comparison of the effects of once-daily and twice-daily proton pump inhibitor administration as omeprazole equivalents on the proportion of the day the time the median intragastric pH remained at 4 or higher. Once-a-day proton pump inhibitor therapy ranging from 9 to 64 mg omeprazole equivalents. Twice-daily proton pump inhibitor administration ranged from 18 to 64 mg omeprazole equivalents. For both, the linear regression line is shown. For twice-daily administration the 95% CI is also shown. All data are after at least 5 days of therapy in Western populations. (From Graham and Tansel 2018)

following administration of approximately 70 mg omeprazole equivalents twice daily. These results suggest that (a) the dose of omeprazole typically used in prior studies was insufficient to protect the pancreatic enzymes from inactivation in the stomach, (b) most of the beneficial effects would

likely have been at least partially related to improvement in duodenal pH which prevent inactivation of normally secreted enzymes (i.e., allow residual function to become active) and allow emptied enzyme to function properly, (c) the resulting change in the gastric contents might reduce the separation of the enteric coated beads from the meal in the stomach (which appears very unlikely unless it allowed some of the beads to dissolve in the stomach and release their enzymes) or, (d) improve bead dissolution in the proximal intestine.

As noted previously, if the intragastric pH remains high, unprotected enzymes are highly effective in reducing both steatorrhea and creatorrhea (Graham 1977). This degree of pH control is possible but to reliably achieve this probably requires twice daily proton pump inhibitor therapy as well as adjuvant antacids to neutralize the small amount of acid still being produced (Graham and Tansel 2018; Julapalli and Graham 2005) (Fig. 14.5). While the optimum doses of PPI and antacid for this indication have yet to be determined, we recommend that proof of principle experiments administer 60 or more mg omeprazole equivalents (e.g., 40 mg of esomeprazole or rabeprazole twice daily) which would be expected to provide a median pH4time of approximately 85%. This high dose of proton pump inhibitors can significantly inhibit acid secretion allowing very small amounts of antacid to have a profound and long lasting effect. Based on the data from prior studies, we would start with sodium bicarbonate (1.3 g; 12 mEq) or aluminum hydroxide (5 or 10 mL; 10 or 20 mEq) at the beginning and end of the meal, and possibly 1 and 3 h after the meal, for initial experiments with unprotected enzymes (Graham 1982). Subsequent experiments designed to identify the optimum proton pump inhibitor and antacid dosages and frequencies of administration and should also include measurements of fecal fat and intragastric pH. Possibly, the new and more potent and long acting competitive potassium blocker, vonoprazan alone would suffice without adjuvant antacids (Graham and Dore 2018).

14.3.8 Summary and Recommendations for Use of Enzymes

Our recommended approach to management of pancreatic insufficiency is illustrated in Fig. 14.6. Although it is recommended that one take into account the patient's diet and level of pancreatic insufficiency, these are hard to estimate and there is no evidence that they are actually important factors. We suggest starting with 18,000–30,000 USP units of lipase per meal with an enteric coated microbead product given in divided doses (e.g., before, at the beginning and mid-meal). Multiple administrations of enzymes to achieve the total dose are designed to achieve better coordination of enzyme and meal delivery to the duodenum (discussed in detail in reference (Trang et al.)). The most common approach to assessing effectiveness has been by patients' reported response and symptoms (Dominguez-Munoz 2011; Dominguez-Munoz and Iglesias-Garcia 2010). This is highly unreliable but repeated fecal fat or ^{13}C-mixed triglyceride breath testing are generally unavailable often making symptomatic assessment the only currently available practical approach for many clinicians. If there is an unsatisfactory response, increasing the enzyme (e.g., doubling the amount to a total of 50,000 or 60,000 units) is typically the next step but, as discussed above, one can expect little or no dose-response effect, such that the strategy is unlikely to be successful and likely only increases costs and side effects (da la Iglesia-García et al. 2017; Trang et al. 2014). An inadequate response to the initial dose of enzymes should prompt reconsideration of the presence of more than one diagnosis (Fig. 14.6). An alternate approach to increasing the dosage above 50,000–60,000 lipase units/meal is to instead add or substitute a non-enteric coated enzyme product just before or at the beginning of the meal (e.g., Viokace®). Probably a better alternative is to switch entirely to non-enteric coated enzymes along with reliable suppression of gastric acidity (Fig. 14.6) as described above (e.g., approximately 60 mg omeprazole equivalents BID and adjuvant antacids such as sodium bicarbonate or aluminum hydroxide).

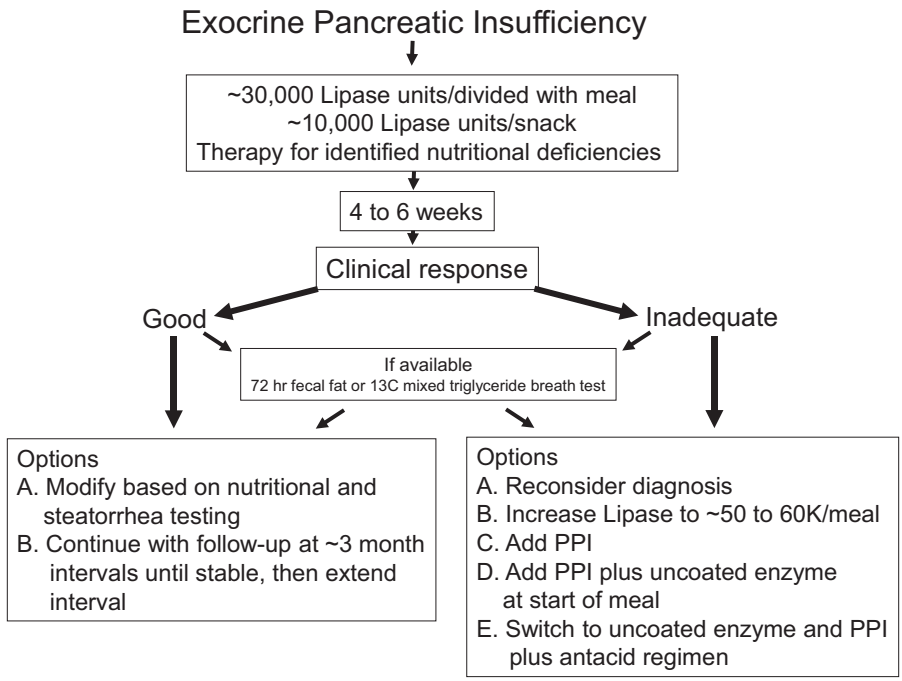

Fig. 14.6 Algorithm describing the recommended clinical approach to using replacement enzymes for the treatment of exocrine pancreatic insufficiency

This approach has not been tested with current formulations but treatment of those with low to absent gastric secretion with uncoated enzymes has proven highly successful in the past. With this approach enzymes should be taken immediately before and throughout the meal to ensure their mixing and emptying with the meal.

14.4 Chronic Pancreatitis

14.4.1 Nutritional Assessment of Patients with Chronic Pancreatitis

Chronic pancreatitis is associated with both endocrine and exocrine insufficiency. Patients with both endocrine and exocrine insufficiencies are particularly difficult to manage as they have difficulty absorbing ingested nutrients and in addition to malabsorption also experience calorie loss via urinary excretion of sugar. In these patients controlling blood sugar is often very difficult until malabsorption is controlled. Weight loss, symptoms associated with maldigestion and difficulty in controlling sugar are common presentations of pancreatic insufficiency. The focus on improving overall nutrition often does not receive the same attention in the literature or in practice as details regarding pancreatic enzymes replacement. Recent longitudinal cohort studies of patients with pancreatic insufficiency followed long term have also confirmed that there is an increased risk of mortality associated with chronic pancreatitis and that the mortality risk and poorest quality of life is greatest among those with low body mass index (da la Iglesia-García et al. 2018; Duggan et al. 2014). In recent studies, many patients with pancreatic insufficiency are either overweight or obese yet they demonstrate reduced functional capacity such as assessed by hand grip strength and muscle mass (Duggan et al. 2014).

Fecal elastase I levels do not relate to the presence or absence of micronutrient deficiencies and should not be used to guide whether deficiencies are present or whether one should evaluate micronutrient status. Nutritional deficiencies are com-

mon in patients with pancreatic insufficiency and we recommend that micronutrient status should be routinely and regularly assessed (Duggan et al. 2014). In the past, vitamin deficiencies were very common in this group of patients. Recent studies have confirmed that the problem remains although the prevalence of vitamin deficiencies is lower (Duggan et al. 2014). For example, a prospective study of 40 patients with chronic pancreatitis, many on treatment, found deficiencies of vitamin K (63%), vitamin D (53%), vitamin E (10%) and vitamin A (3%) as well as osteopenia (45%) and osteoporosis (10%) (Sikkens et al. 2013). Another study of those on long term treatment found vitamin A and D deficiencies in 14.5% and 24.5%, respectively (Duggan et al. 2014). However, some of these patients had excess vitamin A levels in the toxic range confirming the need for testing. Another recent study confirmed low levels of magnesium, hemoglobin, albumin, prealbumin, and retinol binding protein in patients with pancreatic insufficiency (Lindkvist et al. 2012). In that study a low serum magnesium (<2.05 mg/dL) highly correlated with the presence of pancreatic exocrine insufficiency. As noted earlier, both calcium and magnesium bind with fatty acids to form poorly soluble calcium or magnesium soaps and are malabsorbed resulting in hypomagnesemia and reduced bone density (Graham and Sackman 1982, 1983). This interaction requires calcium and magnesium replacement be separated from meals where the presence of calcium and magnesium could also interfere with fat absorption.

14.4.2 Recommended Testing for Vitamin Deficiencies and Nutritional Status

Evaluation of patients with pancreatic insufficiency should include anthropomorphic measurements and regular testing for specific nutritional deficiencies (Lindkvist et al. 2012). Hand strength testing is simple and is recommended. Initial testing will serve to identify if and which specific deficiencies are present and allow a patient-specific replacement strategy to be developed. Further testing is then required to ensure the deficiencies are corrected and hypervitaminoses do not occur. Regular assistance of a trained dietitian is extremely useful but not a guarantee of success (Sikkens et al. 2012). There are no recent high quality evidenced-based guideline defining which tests should be done or how often. Routine follow-up measurement of serum vitamin E, magnesium, and plasma proteins, notably retinol binding protein, albumin, and prealbumin levels has been recommended (Lindkvist et al. 2015).

The blood tests often used to assess nutritional status in pancreatic insufficiency are shown in Table 14.5. Initial nutritional status screening should be conducted at the time of diagnosis. We recommend that levels be rechecked after 3 months of starting enzyme replacement therapy and, if normal, subsequent testing of nutritional status should be done annually. More frequent laboratory testing should be individualized based on tolerance of oral feeding, whether high dosage vitamin supplementation (vitamin replacement therapy) has been instituted, and in the presence of continuing steatorrhea, nausea, vomiting or weight loss. The fat soluble vitamins (A, D, E, and K) are especially prone to being deficient. Among those with deficiency, vitamin D and E are most likely to be deficient.

The most dramatic manifestation of vitamin A deficiency is night blindness (i.e., Do you have difficulty driving at night?), however vitamin A deficiency is currently uncommonly seen in pancreatic insufficient patients (Duggan et al. 2014). Biochemical assessment of vitamin A involves measuring retinol binding protein and prealbumin (transthretin). Retinyl esters normally bind to retinol binding protein and prealbumin and are transported from the liver to the tissues. Retinol binding protein is a negative acute phase protein and thus levels fall during infection and inflammation. It has been suggested that rather than rely entirely on measurement of retinol binding protein, a better measure of vitamin A status is to assess the retinol binding protein:prealbumin ratio: a ratio of $\leq$0.36 is indicative of vitamin A deficiency (Rogers 2013). Zinc is required for synthesis of retinol binding protein such that failure to respond to supplemen-

Table 14.5 Recommended laboratory test for nutritional assessment, daily allowances and replacement recommendations

Test	Normal	Daily	Replacement
Vitamin A	32.5–78 μg/dL	10,000 IU	20,000 IU
Retinol binding protein (RBP)	1.6–6 mg/dL		
Prealbumin	16–30 mg/dL		
RBP:prealbumin ratio	≤0.36		
Vitamin D		800–2000 IU	1600–10,000 IU
25-hydroxy vitamin D	20–60 ng/mL		
Vitamin E	5.5–17.0 mg/L	200–400 IU	800–12,000 IU
Serum α-tocopherol	>0.7 ml/dL		
α-tocopherol:cholesterol ratio	<2.47 mg/g		
Vitamin K		300–500 μg	5–10 mg/week
INR (international normalized ratio)	<1.1		
Vitamin B12	200–800 pg/mL		
Magnesium	1.6–2.6 mEq/L		
Zinc	75–140 μg/dL		
Albumin	3.5–5.5 g/dL		
Cholesterol	<200 mg/dL		

ABIM Laboratory Test Reference Ranges January 2018

tal vitamin A suggests zinc deficiency. During replacement it is important that one avoid hypervitaminosis A which can manifest as nausea, vomiting, anorexia, and bone pain. Generally, one should recheck levels more often during high dose vitamin A replacement therapy. As noted above, in one study of patients on enzyme therapy, hypervitaminosis A was more common than deficiency (Duggan et al. 2014).

Vitamin D deficiency is especially common in chronic pancreatic insufficiency but it is also common in the general population. The recommendation is to provide 1500–2000 IU daily for those over 18 years of age with a low 25 hydroxy vitamin D level ≥20 but ≤30 ng/mL and increase the daily dose by 1600–6000 IU of vitamin D3 (Borowitz et al. 2002; Rogers 2013). Those with levels <20 ng/mL should receive 10,000 IU/day vitamin D3 for 3 months before rechecking levels and modifying treatment as required (Borowitz and Gelfond 2013). Because metabolic bone disease is a common problem in patients with pancreatic insufficiency periodic bone densitometry is recommended (Bernstein et al. 2003).

Vitamin E is an antioxidant and is assessed as serum α-tocopherol levels (normal >0.7 ml/dL). Vitamin E deficiency is one of the most common fat soluble vitamin deficiencies seen in pancreatic insufficiency. Serum levels correlate with plasma lipid levels such that an α-tocopherol:cholesterol ratio of <2.47 mg/g is considered indicative of deficiency. Vitamin K level is reflected by the prothrombin level usually assessed as the International Normalized Ratio (INR).

Vitamin B-12 deficiency may also be seen as pancreatic trypsin is required to dissociate intrinsic factor from R protein and make vitamin B12 available for absorption. Folate is usually normal but if folate and vitamin C levels are available, we recommend they also be checked initially.

14.4.3 Water-Miscible Replacement Vitamins

Vitamin dosing levels for adults are show in Table 14.5. While in children with cystic fibrosis many recommend water-miscible vitamins, water miscible vitamins are not necessary for adult patients on pancreatic enzyme replacement therapy. For those interested in acquiring water miscible vitamin preparations, data on individual preparations and their composition is available from the Cystic Fibrosis Foundation (https://www.cff.org/Life-With-CF/Daily-Life/Fitness-

and-Nutrition/Nutrition/Getting-Your-Nutrients/Vitamin-Comparison-Chart-for-CF-Specific-Multivitamins.pdf). Water-miscible fat-soluble vitamins are available from Aptalis (http://store.foundcare.com/aptalis/product/aquadeks-chewable-tablets/) as SourceCF or AquaADEK, or from Shear/Kershman laboratories as VITAMAX.

14.4.4 Enzymes for Treatment or Prevention of Pancreatic Pain

The management of pain in chronic pancreatitis is clinically challenging in part because the etiology of pain in this setting is poorly understood (Hobbs et al. 2016). A heterogeneous collection of theories of pancreatic pain abound, including pancreatic ductal obstruction/hypertension secondary to stones and strictures, fibrosis-induced increased interstitial pancreatic pressure, pancreatic ischemia, and pancreatic neuritis (Table 14.6). There are a number of excellent reviews that one can consult for specific details of pathogenesis and therapy (Hobbs et al. 2016; Poulsen et al. 2013). A variety of strategies to treat and prevent pain, some of which address these theories, have been tried (Hobbs et al. 2016). Administration of pancreatic enzymes remain a viable option in specific cases.

Chronic pancreatitis is characterized by ongoing pancreatic inflammation leading to disordered pancreatic structure and function. The characteristic pain of chronic pancreatitis is epigastric, precipitated by food and radiating to the back. One potential cause of pancreatic pain is related to pancreatic ductal hypertension attributed to inflammatory strictures or obstructing stones. Many studies have shown improvement of pain with decompression of a dilated pancreatic duct (Hobbs et al. 2016). However, ductal hypertension causing interstitial hypertension is not present in many with painful chronic pancreatitis and the pain is thought instead to be related to pancreatic ischemia and neuritis (Hobbs et al. 2016).

Some patients have chronic pancreatitis pain responsive to pancreatic enzyme therapy. Pain associated with malabsorption can also arise from the presence of digestive products in the gastrointestinal tract and correction of malabsorption will reduce or eliminate this pain (Hobbs et al. 2016). A second mechanism for pain reduction is to prevent increased pancreatic pressure by feedback inhibition of pancreatic secretion.

Table 14.6 Mechanisms of pain in chronic pancreatitis

Increased intraductal pressure
Ductal obstruction from strictures/stones
Increased intrapancreatic pressure (compartment-like syndrome)
Fibrosis causing lack of distensibility
Neuropathic
Entrapment of nerves
Damage of nerves by enzymes
Increased nerve tissue
Pancreatic ischemia
Worsened during increased enzyme secretion

14.4.5 Pancreatic Enzymes and Negative Feedback

Observational studies have noted reduction in pancreatic pain with pancreatic enzyme therapy in some patients with chronic pancreatitis (Hobbs et al. 2016). This has been attributed to exogenous pancreatic enzymes reducing endogenous secretion of enzymes in response to meals which reduces the increase in ductal and parenchymal pressure associated with secretion of pancreatic juice and prevents or reduces pain (Hobbs et al. 2016).

The normal human pancreas secretes continuously which increases in the post-prandial period. Entry of food and fatty acids into the duodenum triggers secretion of cholecystokinin (CCK) and secretin which stimulate pancreatic enzyme and bicarbonate secretion (Layer and Keller 1999). Negative pancreatic feedback inhibition has been demonstrated in rats, chickens and pigs (Chernick et al. 1948; Corring 1973; Green and Lyman 1972; Ihse et al. 1979; Louie et al. 1986; Rausch et al. 1987; Shiratori et al. 1986). In healthy humans, pancreatic enzyme output suppression is dose-dependent occurring with the intraduodenal infusion of proteases: the minimum dose is 0.5 mg/mL of trypsin and maximal suppression occurred with 1.0 mg/mL (Owyang et al. 1986a).

Suppression also correlated with the decline in blood CCK levels (Owyang et al. 1986a). It remains unclear how mg of trypsin/mL relate to USP units of protease activity used to describe pancreatic enzymes. The Worthington catalog suggests the conversion is about 3000 USP units/mg bovine trypsin (http://www.worthington-biochem.com/try/cat.html).

Pancreatic outputs have been compared in patients with differing severity of chronic pancreatitis and healthy controls (Slaff et al. 1984) and the infusion of 10 mg/mL of trypsin was found to reduce pancreatic secretion by approximately 32% in patients with reduced pancreatic output vs. 74% in those with normal pancreatic secretion. No inhibition was noted in patients with low pancreatic bicarbonate secretion and steatorrhea (Slaff et al. 1984). However, chronic pancreatic enzyme therapy resulted in a 27% decrease in basal pancreatic secretion compared to a 46% decrease with amino acid stimulated secretion. In that study, the minimum trypsin concentration required to inhibit pancreatic exocrine secretion was 0.9 mg/mL with maximum suppression at 2.5 mg/mL. Chymotrypsin (10 mg/mL) also decreased amino acid-stimulated trypsin output whereas protease-free lipase and amylase have no effect. Overall, the data are consistent with the notions that (a) intraduodenal trypsin and chymotrypsin both suppress human pancreatic secretion, (b) that suppression is minimal in advanced pancreatic insufficiency and (c) patients who fail to suppress pancreatic secretion often do not experience pain relief with enzyme supplementation (Slaff et al. 1984). The data regarding control of pancreatic secretion in human are consistent with several distinct feedback pathways, one mediated by proteases (e.g., trypsin/chymotrypsin) (Adler et al. 1988a, b; Ebbehoj et al. 1990; Liener et al. 1988) and another by acetylcholine (Owyang et al. 1986b).

14.4.6 How Well Does Enzyme Therapy Reduce Pancreatic Pain?

There have been numerous studies and several large meta-analyses of the use of pancreatic enzymes in the treatment of abdominal pain in chronic pancreatitis (Hobbs et al. 2016). The available studies are heterogenous in relation to severity of exocrine insufficiency, etiology of pancreatitis, clinical presentation, presence or absence of narcotic use, and importantly, to enzyme formulation and dosage and relation to meals. Together, these caveats greatly inhibit one's ability to evaluate the effect of enzyme therapy on pain relief. Individual studies have, however, shown reduced pancreatic pain with both enteric and non-enteric coated enzymes compared with placebo and have reported improved quality of life with pancreatic enzymes (Czako et al. 2003; Ramesh et al. 2013).

Overall, the data confirm that some patients with pancreatic pain will respond to enzyme therapy, however, studies showing excellent or good effects are in the minority (Hobbs et al. 2016; Mossner 1991). One issue is that inhibition of pancreatic secretion is protease-specific and requires a threshold concentration of trypsin/chymotrypsin. Most studies have used enteric-coated enzymes which are unlikely to provide sufficient intraduodenal trypsin activity to provide feedback effective inhibition. In addition, most of the patients involved have severe insufficiency and are thus were the least likely group to respond.

While the data regarding use of pancreas enzymes to treat pain in chronic pancreatitis is poor, long term studies have shown improved outcome in terms of absorption and pain relief associated with the use of pancreatic enzymes. This is consistent with pain associated with malabsorption of nutrients being an important and treatable factor (Czako et al. 2003; Gubergrits et al. 2011; Hobbs et al. 2016; Ramesh et al. 2013). Studies with non-enteric coated enzyme preparations given while preventing gastric inactivation are needed to adequately test the role of the negative feedback loop and to rest the pancreas and also provide pain relief.

14.5 Conclusions

The most common uses for pancreatic enzymes are as replacement therapy for treatment of exocrine pancreatic sufficiency and for pain associ-

ated with chronic pancreatitis. Exocrine pancreatic insufficiency is one of the most common causes of malabsorption. The most common etiologies are chronic pancreatitis, cystic fibrosis, and surgical resection. We discuss the details of use of pancreatic enzymes to replace those needed for normal digestion as well as the barriers that must be successfully dealt with to achieve that goal. We also discuss the use of pancreatic enzymes in pancreatic pain and the various mechanisms that may produce pain in chronic pancreatic disease. Finally, we discuss the nutritional deficiencies common in patients with pancreatic insufficiency and the approach to identifying, monitoring, and treating these deficiencies.

The major hurdle to providing successful therapy has been destruction of pancreatic enzymes during transit through the stomach. The introduction of enteric coated enzymes packages as microspheres helped overcome this barrier but also proved to have significant limitations in that the microspheres tend to separate from the meal and empty separately, introducing a new barrier. In the natural process, the enzymes and meal are mixed along with bile salts at the proper pH to maximize digestion and absorption. Separation of the microspheres from the meal and their slow dissolution results in a new barrier made worse by the fact that microspheres may not release their contents until deep within the small intestine. Nonetheless they are partially effective and were more reliable than uncoated enzymes. However, there is no dose response, as increasing the microsphere dosage has minimal or no further effect on efficacy and generally only results in increased costs and side effects. We discuss how to maximize the benefits with microspheres but for most questions there are no clinical trials to confirm improved efficacy such as whether adding non-coated enzymes at the beginning of the meal would improve efficacy.

Until recently it was unknown how to reliably overcome the pH barrier caused by lipase being irreversibly inactivated at pH 4 or below. Recent understandings of relative PPI potency and how best to administer PPIs to maximize the time the intragastric pH remains above four suggests that it should now be possible to utilize non-enteric coated enzymes effectively. For example, administration of 60–70 mg of omeprazole or its equivalent twice-a-day (e.g., 75 mg of lansoprazole, or 40 mg of esomeprazole or rabeprazole twice-a-day) possibly with a small amount of an appropriate antacid (e.g., aluminum hydroxide or sodium bicarbonate) at the beginning and end of the meal or 1 h after the meal should provide a milieu to protect the enzymes, allow mixing and emptying along with the meal, and provide maximum benefit. This hypothesis remains to be tested. In 2004, the FDA mandated that all pancreatic enzymes must prove efficacy and the research has been company-sponsored studies to prove that the new products were superior to placebo. There have been a few company-sponsored studies looking at some important variables, such as microsphere emptying and separation from the meals, but none of those data have been published or made available on request and support for addressing the many clinically important questions noted above remains lacking.

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Competing Interests Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *Helicobacter pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies. Dr. Ketwaroo does not have any relevant disclosures.

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