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FRONTIER

Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21st century

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Abstract

Restitution of normal fat absorption in exocrine pancreatic insufficiency remains an elusive goal. Although many patients achieve satisfactory clinical results with enzyme therapy, few experience normalization of fat absorption, and many, if not most, will require individualized therapy. Increasing the quantity of lipase administered rarely eliminates steatorrhea but increases the cost of therapy. Enteric coated enzyme microbead formulations tend to separate from nutrients in the stomach precluding coordinated emptying of enzymes and nutrients. Unprotected enzymes mix well and empty with nutrients but are inactivated at pH 4 or below. We describe approaches for improving the results of enzyme therapy including changing to, or adding, a different product, adding non-enteric coated enzymes, (*e.g.*, giving unprotected enzymes at the start of the meal and acid-protected formulations later), use of antisecretory drugs and/or antacids, and changing the timing of enzyme administration. Because considerable lipid is emptied in the first postprandial hour, it is prudent to start therapy with enteric coated microbead prior to the meal so that some enzymes are available during that first hour. Patients with hyperacidity may benefit from adjuvant antisecretory therapy to reduce the duodenal acid load and possibly also sodium bicarbonate to prevent duodenal acidity. Comparative studies of clinical effectiveness of different formulations as well as the characteristics of dispersion, emptying, and dissolution of enteric-coated microspheres of different diameter and density are needed; many such studies have been completed but not yet made public. We discuss the history of pancreatic enzyme therapy and describe current use of modern preparations, approaches to overcoming unsatisfactory clinical responses, as well as studies needed to be able to provide reliably effective therapy.

Key words: Pancreatic insufficiency; Pancreatic enzyme replacement therapy; Lipase; Clinical trials; Steatorrhea; Fat malabsorption; Chronic pancreatitis

Core tip: In the last two decades, a number of studies comparing pancreatic enzymes and placebo have confirmed that pancreatic enzymes are superior to placebo for treatment of pancreatic malabsorption. While many patients achieved a satisfactory clinical response, individualization is often needed. Studies conclusively show that dose escalation is not a reliable method of obtaining further improvements and instead results in increased costs. Here, we describe alternate strategies for obtaining a satisfactory clinical response including changing to, or adding, a different product, adding non-enteric coated enzymes, use of antisecretory drugs and/or antacids, and changing the timing of enzyme administration.

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Dr. Graham is internationally recognized for his expertise in medicine and gastroenterology and is the author of more than 900 scientific papers, several books, and more than 100 chapters in medical text books. One of his papers is listed as one of the three most important papers in gastroenterology in the first 80 years of the *Annals of Internal Medicine*: (*i.e.*, Landmark Papers in Internal Medicine: The First 80 Years of Annals of Internal Medicine. Harold C Sox and Edward J Huth (Eds), 2009 (paper cited: Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Ann Intern Med* 1992; 116: 705-8.).

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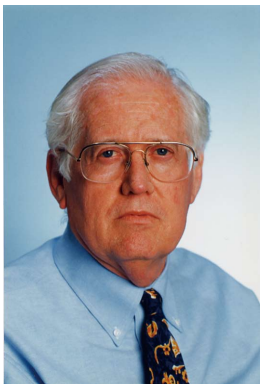

Figure 1 David Y Graham, MD, Professor, Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, 2002 Holcombe Blvd, Houston, TX 77030, United States.

INTRODUCTION

Orally administered pancreatic enzymes have been available since at least the 19th century, when many formulations were available as digestive aids. At that time it was known that orally administered enzymes were destroyed in gastric juice and that they were most effective when given in alkaline media[1]. A review of early 20th century research on the use of pancreatic enzymes for treatment of steatorrhea secondary to exocrine pancreatic insufficiency reported a wide variation in efficacy, yielding an overall 50% approximate reduction in steatorrhea[2]. The goal of pancreatic enzyme therapy is to restore normal fat absorption by delivering "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"[3]. Achieving this goal has remained elusive despite the introduction and use of modern potent enzyme preparations[3-9].

Normal fat absorption requires integration of nutrient delivery with pancreatic and biliary secretions to accomplish hydrolysis and solubilization of ingested fats and fat-soluble dietary constituents. The normal process is finely tuned and requires coordination of many steps including controlled delivery of nutrients to the intestine, neutralization of acidic gastric contents, and secretion of pancreatic enzymes and bile to promote optimal digestion and solubilization of digestive products. These products of digestion then require a sufficient luminal intestinal surface area for absorption. Normally, the intestinal tract is able to process and absorb approximately 95% of ingested fat. There is considerable reserve capacity with all of the elements such that major anatomic alterations are required for weight loss surgery to be effective. The pancreas provides the bulk of the lipase needed for hydrolysis of triglycerides as well as bicarbonate to neutralize the acidic gastric contents. Pancreatic steatorrhea generally does not occur until lipase secretion is reduced by 90% or more[10].

Pancreatic steatorrhea is caused by disruptions of the normal process in which pancreatic enzymes are either inactivated or are otherwise unavailable (*e.g.*, blockage of the pancreatic duct, or resection or destruction of the glandular pancreas). Fungal, plant, and animal (especially

Table 1 Reasons for a poor response to supplemental enzyme therapy

Inactivation of the enzymes in the stomach by acid and/or proteases
Inadequate mixing of the enzymes and nutrients during delivery to the small intestine such that a proportion of the meal is not exposed to appropriate concentrations of enzymes
Separation of enteric-coated microspheres from meal contents in the stomach
Low duodenal and small bowel pH fail to provide optimal conditions for lipase and bile salts to provide optimal digestion of the ingested nutrients
Delayed dissolution of enteric-coated enzyme microspheres in the small intestine
Incorrect or incomplete diagnosis

Table 2 Myths regarding modern microbead enzyme therapy

Currently available formulations will reliably correct steatorrhea
Increasing the dose of microbeads increases the effectiveness
Choice of dose depends on fat content of the diet
Proton pump therapy generally improves success with microbead therapy
Microbeads are fully protected in applesauce
Uncoated enzymes have no place in modern pancreatic enzyme therapy

porcine) pancreatic enzymes are available, and theoretically the simple addition of these enzymes with meals should resolve the deficiency and restore normal absorption. Despite this hypothetical possibility, the administration of large doses of replacement pancreatic enzymes generally has not resulted in complete restoration of normal fat absorption[2,9,11-14].

One early approach was the use of enteric coating to protect the enzymes during passage through the stomach, but this was met with limited success[2,15]. Subsequent studies of normal gastric and pancreatic physiology identified many other barriers to successful treatment with pancreatic enzymes[16,17] (Table 1). This paper discusses the current status and clinical effectiveness of pancreatic enzyme therapy as well as possible approaches to overcoming the barriers to successful therapy. We also discuss the many myths and common misconceptions regarding therapy (Table 2). We begin with a historical review of the use of pancreatic enzyme therapy in the treatment of malabsorption due to chronic pancreatitis and cystic fibrosis; this historical perspective also provides the physiologic basis for the use of supplemental pancreatic enzymes and adjuvant therapies. We focus on overcoming the limitations of common strategies used to improve outcome, such as increasing the amount of lipase per meal, use of enteric-coating, the timing of enzyme administration in relation to meals, and use of antacids and antisecretory drug as adjuvant therapy. Success requires a strategy that is targeted to identify and overcome the specific barriers preventing correction of steatorrhea (Table 1). Currently, many patients achieve a satisfactory clinical response but few experience complete normalization of fat absorption; more than half often require individualized therapy to obtain symptomatic and nutritional relief[3-8].

The review is based on understanding the underlying physiology and the results of clinical trials in patients. It does not seek to comprehensively review all studies but rather to illustrate key principles and to show consistency of the results (typically failures to achieve correction of steatorrhea). Although meta-analyses have confirmed that enzyme therapy is superior to placebo, there is no evidence that one product is superior to another or that any will reliably eliminate steatorrhea. We also do not consider potential alternate indications for pancreatic enzymes such as abdominal pain in patients with chronic pancreatitis[18] or irritable bowel syndrome[19,20].

MODERN ERA OF PANCREATIC ENZYME THERAPY

In 2004 the United States Food and Drug Administration (FDA) issued a requirement for manufacturers of prescription pancreatic enzyme products to submit new drug applications (NDAs) for all pancreatic enzyme products[21]. The FDA provided guidance on the minimal standards regarding the amount and stability of enzymes and the studies needed to establish efficacy (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf). The companies were told that only products receiving a new FDA approval would be allowed to remain on the market by 2008; this was later extended to 2010. The primary efficacy requirement was based on the comparison of the active product with placebo, which set a relatively low bar for efficacy. The FDA also requested, but did not require for approval, additional information about each product in terms of studies addressing gastric emptying, mixing, and dissolution time. The majority of products now available in the United States are enteric coated and formulated as microbeads, microtablets or microspheres (we use the terms "microbeads", "microtablets" and "microspheres" interchangeably). A non-enteric-coated product (Viokaze®, Forest Pharmaceuticals) was approved in 2012 (Table 3).

Most of the formulations are marketed in different strengths based on enzyme activity per capsule or tablet. Increasing the activity/dosage unit has generally been achieved by re-packaging the basic enzyme product into larger capsules, using different diameter enteric-coated beads, or both (Figure 2, Table 3).

The available prescription products are relatively expensive (Table 3). However, because "health food" stores still offer pancreatic enzymes as non-prescription "digestive aids" at a relatively low cost, many patients are likely to also use them. As noted, none of the currently available approved formulations have been shown to reliably achieve normal absorption irrespective of the quantity of lipase administered.

Table 3 Currently available United States Food and Drug Administration approved pancreatic enzyme preparations[1]

DRUG	Stregth Lipase USP	Preparation	Diagmeter\e	pH[1]	Cost per tablet (United States)	Cost per 1000 units
CREON®						
Creon 3000	3000	Capsule with enteric coated minimicrospheres	0.71-1.6 mm	5.5	$1.18	$0.39
Creon 6000	6000	Capsule with enteric coated minimicrospheres	0.71-1.6 mm	5.5	$1.30	$0.22
Creon 12000	12000	Capsule with enteric coated minimicrospheres	0.71-1.6 mm	5.5	$2.32	$0.19
Creon 24000	24000	Capsule with enteric coated minimicrospheres	0.71-1.6 mm	5.5	$4.56	$0.19
Creon 36000	36000	Capsule with enteric coated minimicrospheres	0.71-1.6 mm	5.5	$7.90	$0.22
Pancreaze®						
Pancreaze 4200	4200	Capsule with enteric coated microtablets	2 mm	5.5	$0.92	$0.22
Pancreaze 10500	10500	Capsule with enteric coated microtablets	2 mm	5.5	$2.29	$0.22
Pancreaze 16800	16800	Capsule with enteric coated microtablets	2 mm	5.5	$3.68	$0.22
Pancreaze 21000	21000	Capsule with enteric coated microtablets	2 mm	5.5	$4.58	$0.22
Zenpep®						
Zenpep 3000	3000	Capsule with enteric coated beads	1.8-1.9 mm	5.5	$1.27	$0.42
Zenpep 5000	5000	Capsule with enteric coated beads	1.8-1.9 mm	5.5	$1.21	$0.24
Zenpep 10000	10000	Capsule with enteric coated beads	2.2-2.5 mm	5.5	$2.39	$0.24
Zenpep 15000	15000	Capsule with enteric coated beads	2.2-2.5 mm	5.5	$3.47	$0.23
Zenpep 20000	20000	Capsule with enteric coated beads	2.2-2.5 mm	5.5	$4.71	$0.24
Zenpep 25000	25000	Capsule with enteric coated beads	2.2-2.5 mm	5.5	$5.83	$0.23
Ultresa®						
Ultresa 13800	13800	Capsule with enteric coated minitablet	2 mm	5.5	$3.01	$0.22
Ultresa 20700	20700	Capsule with enteric coated minitablet	2 mm	5.5	$4.46	$0.22
Ultresa 23000	23000	Capsule with enteric coated minitablet	2 mm	5.5	$5.47	$0.24
Pertyze®						
Pertyze 8000	8000	Capsule with bicarbonate buffered enteric coated microsphere	0.8-2.2 mm	5.5	$1.99	$0.25
Pertyze 16000	16000	Capsule with bicarbonate buffered enteric coated microsphere	0.8-2.2 mm	5.5	$3.99	$0.25
Viokase®						
Viokase 10440	10440	Non-enteric coated			$2.92	$0.28
Viokase 20800	20880	Non-enteric coated			$5.76	$0.28

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

QUANTITY OF LIPASE REQUIRED TO ABOLISH STEATORRHEA

Normal pancreas

Normally, lipase is secreted early in the postprandial period and reaches a maximum within the first hour; the majority of fat digestion and absorption normally occurs within the proximal small intestine[22]. The ability to measure lipase activity led investigators to ask whether there was a best, appropriate, or minimum amount of lipase needed to correct steatorrhea. The available data are confusing in part because lipase units are often presented in different units, making direct comparisons difficult. Many basic and clinical studies use either international units (IU) or United States Pharmacopeia (USP) units. Commercial products in the United States are rated in USP units (1 IU = 3 USP units). We will provide the results whenever possible in USP units. When the units are not clear (as in some older papers) we will simply state the units as lipase units or provide the units name used for that study. The strength of current products ranges from 3000 USP units to 36000 USP units of lipase per dosage unit (*e.g.*, per capsule) (corresponding to a range of 1000 to 12000 IU) (Table 3). The amount of postprandial lipase secreted under normal physiologic circumstances has been estimated at between 9000 to 18000 USP units/min[22,23] Measurements from a patient with a pancreatic fistula suggested that a 60 kg man would produce 192000 Cherry-Crandall units[24]. Overall, the results of such studies depend on the experimental methodology and may explain the wide variation noted[25]. As noted previously, the pancreas has a tremendous reserve capacity, and perfusion studies have

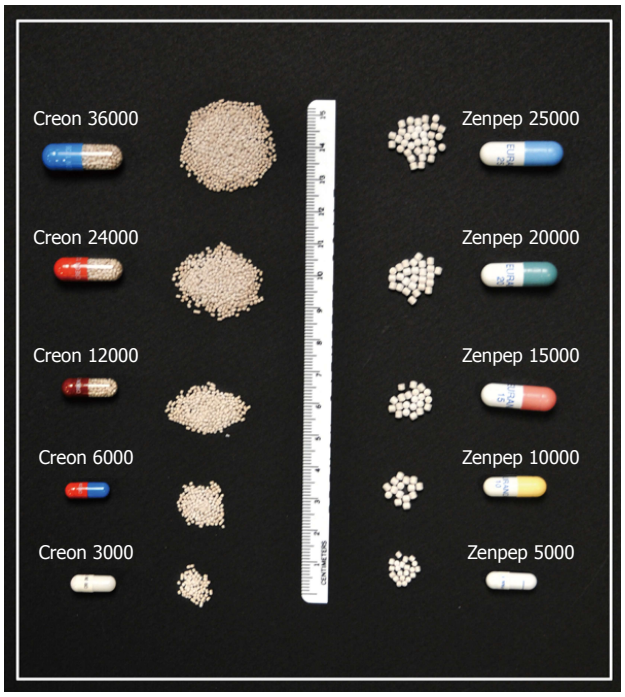

Figure 2 Pancreatic enzyme capsule size and contents increase as the pancreatic enzyme preparation dosage increases, suggesting that dose/unit increases are achieved by packaging the same basic pancreatic enzyme formulation into a larger capsule and/or larger beads.

suggested that approximately 5% of normal output is the threshold to maintain normal fat absorption[26]. Other studies report somewhat higher amounts[10,27].

Clinical results

Because it is difficult or even impossible to exactly simulate the normal integrated response of gastric emptying and pancreatobiliary secretion, estimates of the amount of lipase required to prevent steatorrhea are best determined clinically based on results of clinical trials. Trials using unprotected enzymes theoretically provide the most useful clinical measure, as they provide real time examples of pancreatic enzymes mixing and emptying with ingested nutrients coordinated with the function of the small intestine. However, interpretation of such studies is complicated by intragastric destruction of administered enzymes and by acidification of the duodenum, both of which can inactivate lipase and precipitate bile acids. Nonetheless, the available results probably provide our best estimates.

We performed studies with patients with varying degrees of acid secretory capacity and showed that we could abolish steatorrhea with approximately 30000 USP units of unprotected lipase given with meals (discussed in more detail in the section on the gastric pH barrier below). That study showed that a relatively small quantity of lipase was sufficient as long as the enzymes were able to mix with the meal and the lipase was not destroyed by gastric acidity (Figure 3)[28]. In a subsequent study with an enteric coated preparation, 2 of 6 patients experienced

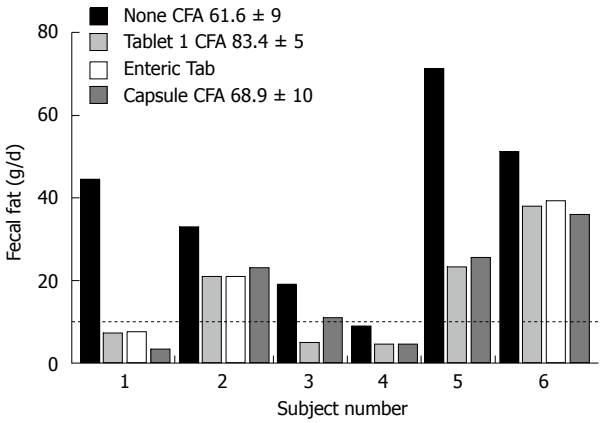

Figure 3 Results of different pancreatic enzyme preparations, tablets, enteric-coated tablets, and capsule in adults with exocrine pancreatic insufficiency. Approximately 30000 USP units of lipase were given with meals. Steatorrhea was corrected in those with low acid secretion. From[28] with permission.

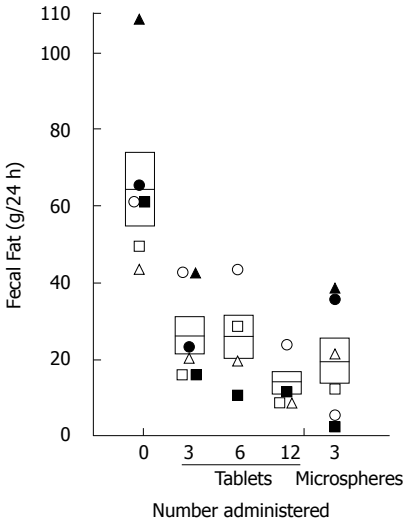

Figure 4 Effect of increasing the enzyme dosage on fecal fat excretion on a 100 gram fat diet. Enzymes were given 3 times per day with meals providing approximately 30000, 60000, or 120000 USP lipase units with each meal or as 18000 USP lipase units as enteric coated microspheres (*i.e.*, 3 tablets, 6 tablets or 12 tablets and 3 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. From[29] with permission.

complete resolution of steatorrhea with only 18000 USP units of lipase with each meal when the enzyme was administered throughout the meal as enteric-coated microspheres (Figure 4)[29]. Overall, it seems reasonable to conclude that between 18000 and 30000 USP units of lipase per meal will result in resolution of steatorrhea, provided that lipase is delivered to the small intestine along with the nutrients and that low gastric and duodenal pH are not present. Achieving these coordinated events, however, 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"[3] (Table 2) has proven difficult.

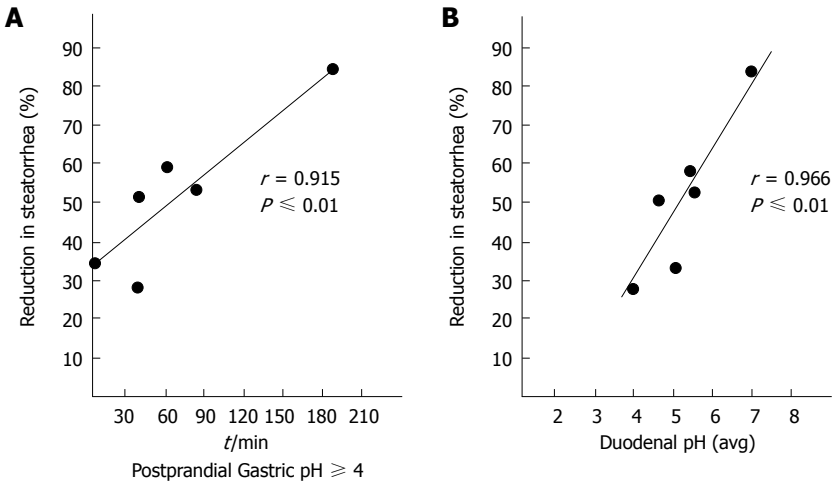

Figure 5 Correlation between percentage reduction in steatorrhea based on the median obtained with 30000 USP units of lipase given in tablets or capsules compared with the time of the postprandial gastric pH was > 4 (A) and in those same subjects compared with the mean post prandial duodenal pH (B). From[28] with permission.

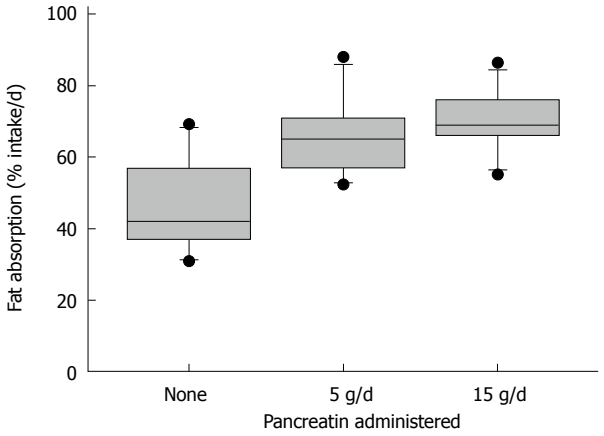

Figure 6 Results of a study comparing the response of enteric coated pancreatic enzyme in a cystic fibrosis patient population. Different doses of enteric coated pancreatic enzymes were taken four times daily immediately before meals and the corresponding average % fat absorption/d[11].

Gastric pH barrier

Lipase is irreversibly inactivated at a pH of 4 or less. Trypsin and the other enzymes are more acid stable but are also destroyed by pepsin in an acid environment[30,31]. Reliable enzyme therapy is therefore easiest to achieve in achlorhydric patients where the gastric pH barrier is absent. For example, we compared different enzyme formulations (2 tablet formulations and one capsule formulation produced by three different manufacturers, including one enteric coated tablet) in 6 patients who varied greatly in terms of their ability to produce acid[28]. The enteric coated tablet was effective only in one subject who also had hypo-/achlorhydria. We assessed the gastric barrier as the average time the gastric pH remained above 4 and the small intestinal pH barrier as the mean duodenal pH during meals. The effect of therapy on steatorrhea was almost identical for each individual subject (Figure 3) but varied between individuals with respect to gastric and duodenal acidity (*i.e.*, increasing acidity had a negative effect on reducing steatorrhea) (Figure 5)[28].

In subsequent studies with a different set of subjects, we examined whether the traditional approach of increasing the amount of unprotected enzymes would improve the effectiveness of therapy (in essence-was there a dose-response effect?)[29]. Doubling the amount of lipase from approximately 30000 USP units per meal to 60000 USP units per meal did not provide an improvement in fat malabsorption (Figure 4). However, quadrupling the lipase dose to 120000 USP (*i.e.*, 12 tablets per meal) did result in improvement in fat absorption (*i.e.,* decreased fat loss) but in only 2 of the 4 subjects tested (Figure 4). Importantly, none of these subjects had resolution of steatorrhea. As noted previously, in another study with different subjects, administration of only 18000 IU of lipase/day as an enteric-coated microbead preparation resulted in resolution of steatorrhea in 2 of the 6 subjects tested (Figure 4)[30].

As unprotected enzymes likely mix well with the nutrients, their effectiveness depends more on acid secretion and gastric emptying than on the quantity administered[30,32-34]. The window of effective unprotected enzyme therapy is defined as the time between ingestion and the time at which the gastric pH falls below 4 which inactivates lipase. Gastric contents tend to layer with the lowest pH being concentrated at the periphery of the meal. Thus, any lipase within the bulk meal may be protected and remain active, but will be inactivated upon mixing with acid contents in the antrum during emptying into the small intestine. Overall, our results confirmed longstanding clinical experience that, although increasing the amount of enzyme administrated may result in an improvement in fat absorption, it generally will not consistently eliminate steatorrhea (Figure 6)[11,12,29,35].

GASTRIC EMPTYING AS A BARRIER TO SUCCESSFUL PANCREATIC ENZYME THERAPY

The initial barrier is the acidic gastric environment that can inactivate pancreatic enzymes. The enzymes also must also mix with the nutrients to be delivered together to the duodenum. The normal gastric antrum grinds and returns food to the body of the stomach. Most nutrients

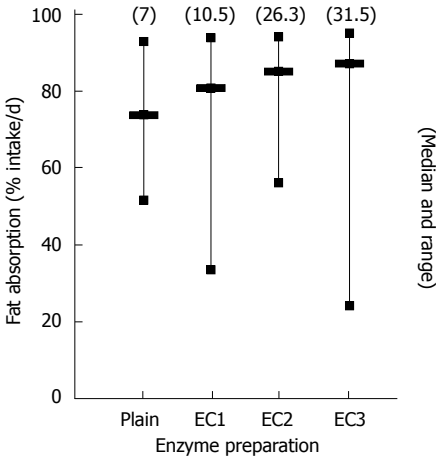

Figure 7 Randomized cross-over study in patients with cystic fibrosis and pancreatic insufficiency that compared plain uncoated enzymes (Pancrex V Forte *n* = 14) and 3 different enteric coated preparations [EC1:Pancreatin Merk, EC2: Creon and EC3: Pancrease (*n* = 19)] using the same lipase dosage. The median and range are shown of fecal fat absorption. With the numbers above the columns ( ) indicating the percent of patients with > 90% fat absorption. None reliably resulted in normalization of fat malabsorption[42].

are emptied as small particles (< 1 mm) suspended within the liquid layer[36]. Depending on their size and density, enzyme microspheres may separate from bulk nutrients and empty separately, thus impeding the interactions critical for digestion[37-39]. Normally, the stomach sieves and retains large particles until after the meal is emptied. This sieving occurs both in the proximal and distal stomach[36,37,40,41]. Currently available enteric coated enzyme beads vary with respect to enzyme content and diameter (*i.e.*, larger doses contain more units of enzyme per bead and may reach up to 2.5 mm in diameter) (Table 3). The dissolution and emptying characteristics of the different enzyme preparations and sizes remains unknown, as the FDA-requested studies have yet to be published. However, based on prior studies, each preparation is likely to have a different emptying profile. There is limited information available regarding the dispersion and emptying of enteric coated microspheres of different diameter and density, particularly in relation to fat malabsorption in humans. Comparative studies of 4 older preparations (Pancrex V Forte, Pancreatin Merk, Creon and Pancrease) showed differences in effectiveness, but it remains unknown whether the differences were primarily related to differences in the emptying of the beads or related to other factors (Figure 7)[42].

The ideal therapy is one that coordinates emptying of the meal and pancreatic enzymes. A significant proportion of ingested fat is emptied during the first hour of the meal, and normal physiologic lipase secretion is highest during this time[38,43-45]. However, enteric coated enzyme microbeads administered with meals tend to remain in the proximal stomach during the first hour, allowing a considerable proportion of fat to escape contact with enzymes and thus escape digestion[38,44]. Gastric emptying of enzymes and nutrients is better coordinated after the first hour, which is likely responsible for the improvement in absorption seen[38,44].

Overall, it is likely that a mismatch of emptying of fat and enzymes is a major contributor to the failure of currently available microbead preparations to fully correct steatorrhea. Bruno *et al*[39] administered microbeads before meals and noted that they separated from the meal and tended to clump in the antrum, although some of the beads emptied even prior to the meal. This finding suggests that one approach to improving therapy is to optimize the timing of the administration of microbeads to reduce or eliminate periods of dissociation of emptying of fat and microbeads.

Although the FDA requested that companies perform studies regarding kinetics of enzyme release of approved products (namely, the when, where, and how much enzyme is released), none of the studies performed to date have yet to be published (*e.g.*, clinicalTrials.gov NCT00676702, Pancrease MT, Johnson and Johnson Pharmaceutical, NJ, United States; NCT00744250, NCT00749099 Pancrecarb MS16, Digestive Care, PA, United States; NCT00559052, Viokase 16, Axcan Pharma, Canada). We requested this and other information such as the median and range of fat absorption from each manufacturer; however, the manufacturers were unresponsive. Importantly, no head to head comparative studies of current FDA approved products from different manufacturers or different formulations of a single product are available. It therefore remains unclear how much, if any, interchangeability there may be between or even within products. It is also not known whether the source of porcine pancreatic enzymes used by different manufactures comes from one or a number of sources.

SMALL INTESTINAL PH BARRIER

Normal lipid digestion and absorption involves hydrolysis of triglycerides as well as solubilization of the products of digestion for subsequent absorption[46,47]. These processes are pH dependent and are disrupted when pancreatic bicarbonate secretion fails to neutralize acidic gastric contents and prevent lipase inactivation and precipitation of glycine conjugated bile salts. In some patients this low pH environment extends far down the small intestine and impairs both digestion and solubilization[13,46,48]. In addition, enteric coated microbeads are designed to dissolve only when intraluminal pH is 5.5 or higher and may not dissolve until reaching the distal small intestine or even the colon[27,33,49-54].

USE OF ANTACIDS AND/OR ANTISECRETORY DRUGS TO EXTEND THE HIGH PH WINDOW

Successful use of unprotected enzymes requires the ability to prevent or reduce inactivation of administered lipase by gastric acid. Antacids have been used for this purpose since the 19th century. More recently the strategy

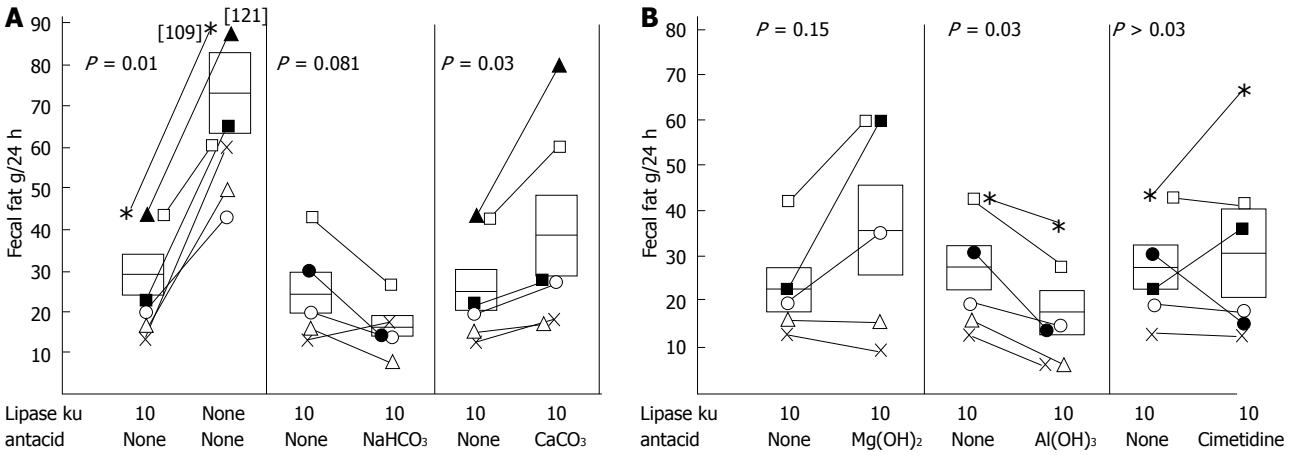

Figure 8 Effect of antacids and enzymes on the effectiveness of 30000 USP units of lipase per meal for the treatment of pancreatic steatorrhea. Each symbol represents a different patient. Sodium bicarbonate, magnesium aluminum hydroxide, aluminum hydroxide, or calcium carbonate were administered at the beginning and the termination of each meal. Cimetidine was given 30 min prior to the meal. From[58] with permission.

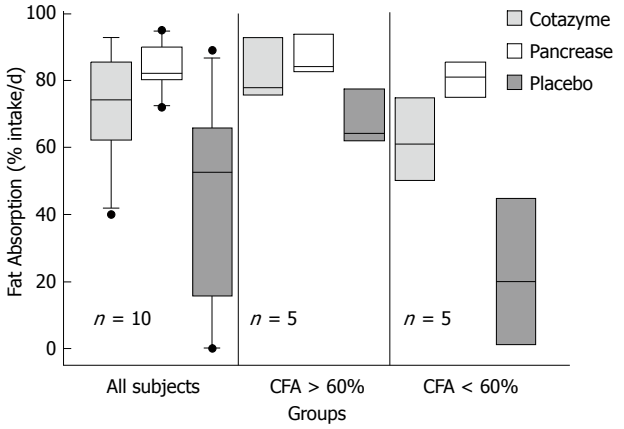

Figure 9 Randomized cross-over comparison of similar amounts of lipase administered as unprotected capsule (Cotazyme®) or enteric coated microspheres (Pancrease®) in cystic fibrosis patients with pancreatic insufficiency. Although the enteric coated preparation was better in those with the greatest degree of malabsorption, neither resulted in resolution of steatorrhea[61].

has shifted to antisecretory drugs; however, a combination of both may be the best option. The strategy to prevent inactivation of lipase differs from treatment of acid peptic disease. In peptic ulcer disease, the goal is to reduce gastric and duodenal acid load sufficiently to eliminate pain and heal the ulcer. In contrast, protection of lipase requires the much more stringent target that the gastric pH never fall to 4 or below (Table 2).

Early investigators reported only limited success in improving the effectiveness of enzyme therapy with co-administration of sodium bicarbonate or aluminum hydroxide[27,32,48,55-57]. We compared different antacids and the antisecretory drug cimetidine for their ability to improve the outcome of therapy with unprotected pancreatic enzymes[58]. We randomized subjects who had an incomplete response to 30000 USP units lipase per meal to receive commonly used doses of sodium bicarbonate (1.3 g; 12 mEq), aluminum hydroxide (30 mL; 57 mEq), magnesium-aluminum hydroxide (30 mL; 72 mEq), or calcium carbonate (1 g; 21 mEq). Each antacid was administered before and immediately after each meal (100 g fat per day)[58]. A final randomization was the 300 mg of the H_2-receptor antagonist, cimetidine, given 30 min before meals. Overall, cimetidine had no noticeable effect on fat absorption (Figure 8). In contrast, adjuvant therapy with either sodium bicarbonate or aluminum hydroxide resulted in a further reduction in steatorrhea (Figure 8). Strikingly, the highly effective antacids calcium carbonate and magnesium-aluminum hydroxide tended to reverse the beneficial effects of the enzyme therapy (Figure 8)[58]. Subsequent studies showed that the calcium and magnesium-containing antacids were effective in increasing intragastric and intraduodenal pH and improving the duodenal delivery of lipase and lipolysis[59]. However, both calcium and magnesium reacted with the fatty acids liberated to produce poorly soluble calcium and magnesium soaps that were poorly absorbed[59,60].

ENTERIC-COATING TO OVERCOME THE GASTRIC PH BARRIER

Using enteric coating is useful to bypass the gastric pH barrier and prevent gastric inactivation of pancreatic enzymes. The use of enteric coated microbead/spheres has resulted in more reliable results than had been obtained with enteric coated tablets (Figures 7 and 9)[42,61], but still fails to abolish steatorrhea for most patients[1,11,29,62-67]. The most common reasons given for an inadequate response to modern enteric coated enzyme therapy include: insufficient dosage, dissociation of the emptying of the microbeads and nutrients, premature opening of the microspheres in the stomach allowing intragastric destruction, long dissolution time which shifts the absorption sites distally, and rapid small intestinal transit which reduces mucosal contact time[33,36,37,43,44,51,68,69]. The benefits of modern enteric coated bead therapy appear greatest amongst those with the poorest responses to unprotected enzymes, most likely due to protection against rapid in-

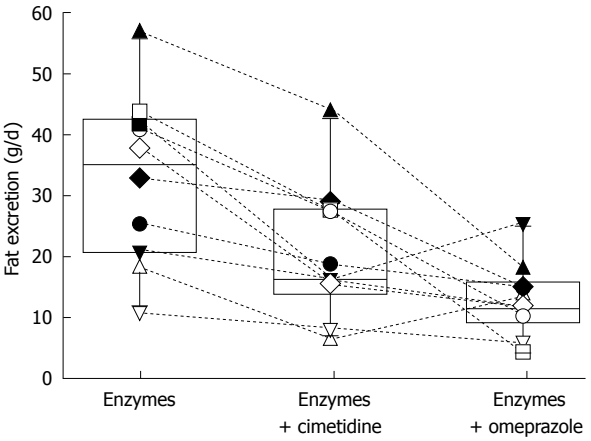

Figure 10 Box plot showing median and 25% and 75% and range for a randomized cross-over study comparing the effect of 1200 mg cimetidine or 60 mg of omeprazole on the effectiveness of pancreatic enzymes. Six tablets of unprotected enzymes (Cotazyme Forte® 36000 FIP units/meal) given 1/2 before meal and 1/2 during the meal). Both antisecretory agents improved outcome but neither reliably resolved steatorrhea. Data from[72].

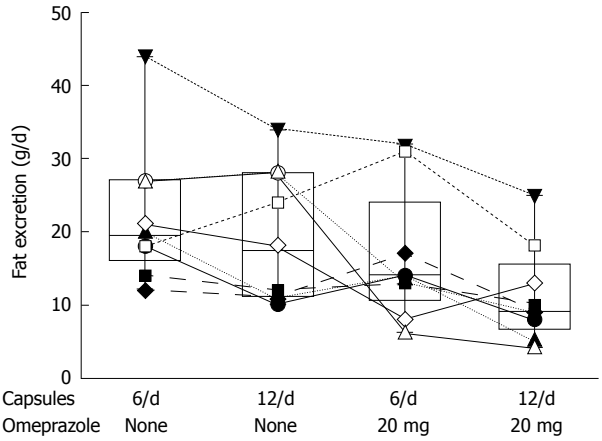

Figure 11 Box plot showing median and 25% to 75% range for a randomized cross-over study comparing the effect of doubling the dose of pancreatic enzyme microspheres (Pancrease®) and the effect of omeprazole in patients with cystic fibrosis and pancreatic insufficiency. Enzymes were taken 1/2 just before and 1/2 after meals. Omeprazole 20 min before breakfast[67].

tragastric inactivation of unprotected lipase[33,42,49,61,66,70,71].

Attempts to improving the efficacy of enteric coated microbead enzyme therapy

Few studies have provided sufficient details to develop hypotheses for testing or insights into why success or failure occurs. The Mayo clinic group tested an early enteric coated microsphere formulation with and without adjuvant acid suppressive therapy[34]. They found that of the 2 of the 6 patients had complete resolution of steatorrhea. Both these patients had high acid secretion and the intragastric pH remained below 5.5. The remaining 4 patients with incomplete responses had higher gastric pH, suggesting that the poor responders may have released the enzymes in the stomach where they were subsequently inactivated when the pH fell[34]. Bruno *et al*[72] compared adjuvant cimetidine or omeprazole with an enteric coated microsphere preparation (Cotazyme Forte®). Normal fat absorption was not observed, but they reported a progressive improvement with increasing suppression of acid secretion (Figure 10), suggesting that antisecretory drugs may be useful adjuvants. A possible mechanism is sufficient reduction of acid secretion to increase the duodenal and small intestinal pH and thus enhance dissolution and effectiveness of enteric coated microbeads[72]. Data to support this hypothesis comes from Regan *et al*[34] who showed that following cimetidine administration, the duodenal pH remained above 6 for up to 200 min postprandial.

The pH burden is related to emptying of acidic gastric contents into the duodenum, which can respond poorly because of abnormal duodenal/pancreatic bicarbonate secretion. Antisecretory drug therapy is potentially most useful in those with gastric acid hypersecretion to reduce the duodenal acid load and allow acid neutralization despite impaired pancreatic secretion of bicarbonate. In one study, Heijerman *et al*[67] compared different doses of enteric coated pancreatic enzymes with and without omeprazole in patients with pancreatic insufficiency due to cystic fibrosis with persistent steatorrhea. Increasing the dose of enzymes did not produce further improvement; however, increasing the enzyme dose and addition of omeprazole did (Figure 11). Overall, most studies with currently available preparations have not shown a consistent benefit for adding antisecretory therapy to enteric coated microbead therapy, except possibly among those with very poor response to enzyme therapy due to high gastric acid secretion[63,72-74]. Recent expert recommendations for use of pancreatic enzymes advise against the routine use of adjuvant proton pump inhibitor therapy[17].

Use of timing of dosing of pancreatic enzymes to improve outcome

In 1959, Jordan *et al*[12] compared 2 regimens in which 8 grams of unprotected enzymes (Viokase®) per day was given in 3 doses with meals or as 8 grams administered hourly from 8 a.m. to 7 p.m. (over 12 h). All 11 patients reduced their fecal fat excretion while taking pancreatic enzyme. Two patients failed to respond to the "with meals" regimen but experienced reductions in fat excretion with the hourly enzyme administration schedule. In contrast, Kalser *et al*[27] reported that administration of enzymes with meals (with adjuvant aluminum hydroxide) or on an hourly basis produced similar results. DiMagno *et al*[13] tested unprotected Viokase® (average of 10551 USP units lipase per tablet) administered either as eight tablets with each meal (2 tablets at the beginning, 4 tablets throughout the meal, followed by 2 tablets at the end of the meal) or as 2 tablets every hour for 4 doses at the onset of meal. In their study, irrespective of the dosing schedule, postprandial gastric pH fell below 4 after 40 min, the duodenal pH fell below 4 after 100 min, and less than 9% of lipase reached the duodenum.

Domínguez-Muñoz *et al*[73] performed a randomized three-way crossover study of 24 patients comparing

40000 USP units of Creon® enteric coated microbeads administered as 4 tablets before meals, 4 tablets just after meals, or 4 tablets throughout meals (as 1 before, 2 during, and 1 tablet after meals). Enzymes were administered only with the 3 main meals of the day given immediately before or after meals or given throughout the meal (as described above, with 10000 USP units before the meal, 20000 USP units during the meal and 10000 USP units after the meal). The authors used the 13C-mixed triglyceride breath test as a surrogate for fat absorption. The percentage of patients who normalized fat digestion was 50%, 54% and 63%, respectively. There were no statistically significant differences and no definitive conclusions can be drawn.

Other issues related to enteric coating

In 1905, Chase wrote that "it is a well-known fact that pancreatin in substance, solution, or simple tablet, is soon rendered inert by the gastric juice when taken into the stomach. The recognition of this fact has led to the manufacture of pills and tablets of pancreatin coated with keratin, salol, *etc*. While such coatings do protect the ferment from the action of gastric juice, it is a question if they are dissolved early enough in the intestine to allow the pancreatin to be of any service in digestion"[15]. The issues raised by Chase in his 1905 review remain unanswered more than 100 years later. Patients with pancreatic insufficiency have alterations in gastro-intestinal motility as well as a reduction in bicarbonate secretion resulting in low intestinal pH, and both of these mechanisms may lead to unpredictable transit and dissolution of the different products. Current formulations are designed to release the enzymes when the pH allows their survival. However, failure to achieve an adequate pH at which dissociation of the coating can occur may delay the site of dissolution to the distal small intestine or even the colon[33,51]. Guarner *et al*[68] compared duodenal and ileal enzyme content of normal controls and patients with pancreatic insufficiency. When normal patients and patients with pancreatic insufficiency received placebo, there was a gradient of higher lipase enzyme activity in the duodenum and lower activity in the ileum. When given enzyme therapy as 5 enteric coated capsules each containing 8000 FIP lipase units (total of 40000 FIP lipase units), the gradient was reversed.

Current enteric coated preparations are available as microspheres or microbeads whose dissolution rate was established using standard FDA-approved *in vitro* dissolution tests. However, little is known about their dissolution or potential differences in dissolution rate *in vivo*, especially at different pH and different luminal environments. Available products generally contain microbeads/spheres of uniform size within a specific dose. However between products and even among products at different doses, the beads may differ in shape, size, and surface area and all of these physical characteristics may affect the kinetics of release of the enzymes[75]. *In vitro* studies such as those described by Löhr *et al*[75] on previously available products would be welcome, especially if the results were directly compared to the results of *in vivo* studies. As noted previously, any data the pharmaceutical companies have has been withheld. Even when or if these data are provided, to be fully useful they must include comparison studies in the same patients to determine the effects of size, shape, differences in coating, or other factors on bioavailability. Such studies may require support by agencies dedicated to exploration of important scientific question without a vested interest that might result in withholding the results.

There are a number of considerations regarding evaluation of the dissolution characteristics of enteric coated enzymes. The rate of dissolution of the enteric coated beads at any particular pH would likely be an important measure in determining where the enzyme is delivered in the small intestine. Aloulou *et al*[51] evaluated the dissolution times in relation to pH of three preparations including the non-coated Eurobiol 12500 and 2 enteric coated preparations, Eurobiol 25000® and Creon 25000®. Uncoated Eurobiol 12500 had essentially instant bioavailability. The half dissolution time of Eurobiol 25000® at pH of 5.2 was 19.2 min, contrasting markedly with Creon 25000® whose half dissolution time at pH of 5.4 was 49.2 minutes. Importantly, this *in vitro* study did not take into account the effect of other confounders such the presence of bile and other substances normally present *in vivo*. Overall bioavailability is likely determined both by the threshold pH of dissociation as well as the rapidity of dissolution.

We tested the dissolution time on Creon 24000®, Zenpep 25000®, and Ultresa 23000® in informal studies using ileal fluid obtained from a patient with an ileostomy. One capsule of each enzyme preparation was placed a 15 mL conical tube containing 7 mL of ileal fluid obtained from a patient with an ileostomy and then centrifuged. The pH was adjusted to approximately 7.5. The experiment was done using a water bath at 38 Celsius. The test tube was manually inverted 3 times every 1.5 min and visually inspected for onset and time to complete dissolution of the capsule. pH was measured at each time interval (Table 4). Each experiment was done in duplicate. The results suggest there are likely differences in dissolution time among the different products and possibly between the same product as different size microbeads. Formal *in vitro* and *in vivo* comparisons are warranted.

Because clinical assessment is a notoriously imprecise measure of effectiveness, a simple, non-invasive measure of overall effectiveness is needed to allow comparisons between and among products[76]. The ^{13}C mixed triglyceride breath test currently appears to be the best option[77,78] as it provides dynamic data regarding gastric emptying, dissolution, and effectiveness of enzyme therapy. It has the added benefit of being simple, non-invasive, inexpensive, and allows for efficient repeated testing of the same subjects. Using a validated breath test allows hypothesis testing and rapid evaluation of different combinations such as timing administration of enzymes in relation to meals, effects of dosage, acid suppression, *etc*. These

Table 4 Dissolution time for pancreatic enzyme in ileal fluid

Pancreatic enzyme	Initial pH	Start to dissolve (min)	Completely dissolved (min)	
Creon® 24000	7.73 pH	9.0	45.8	7.28 pH
Ultresa® 23000	7.52 pH	10.5	30.0	7.48 pH
Zenpep® 25000	7.60 pH	15.0	33.0	7.59 pH

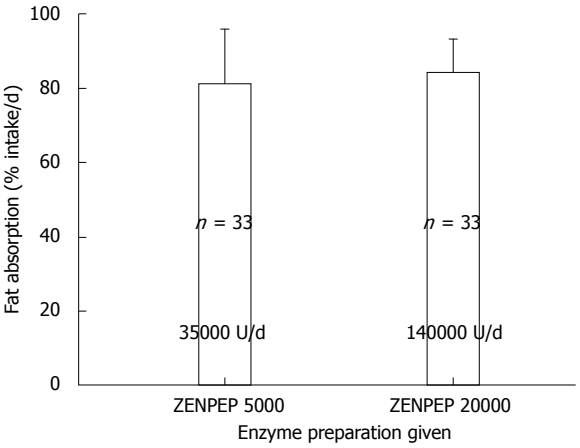

Figure 12 Effect of increasing the dose of enteric coated microbead therapy; seven 5000 USP unit tablets *vs* seven 20000 USP tablets (Zenpep®) on steatorrhea are shown (mean plus standard deviation). Increasing the dosage 4-fold resulted in no significant improvement in steatorrhea and did not result in correction of steatorrhea[4].

overall conclusions could then be tested in a traditional clinical trial. Breath testing also allows for easy and effective monitoring of therapy[77]. Unfortunately, despite being used in research for more than three decades, the test is not widely available outside of Europe and even there it is infrequently used.

APPROACHES TO THERAPY IN 2014-2015

Results with currently FDA approved enzyme preparations

The primary goal of enzyme therapy is to abolish steatorrhea. If this goal cannot be obtained, at the very least, one would like to achieve a coefficient of fat absorption >85% (*e.g.*, 15 g/d on a 100 g fat diet)[17,71]. The mean coefficient of fat absorption with modern enteric coated microspheres based on available data has typically been between 80% and 88% (*i.e.*, such that one third to more than one-half fail to achieve even this minimal desired outcome). Since at least the 19th century, the knee jerk response to inadequate results has been to increase the dosage. The "increase the dosage" strategy has carried over to the use of modern microbead therapy and the availability of high potency products[4,8,79] (Table 3). The published trials with currently available regimens were primarily designed to obtain regulatory approval for new products and for marketing purposes. The studies have therefore used similar protocols based on input from

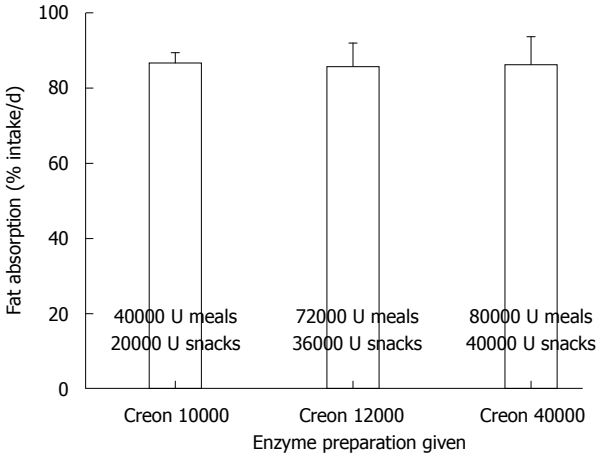

Figure 13 Summary data from 3 different randomized studies of different formulations of an enteric coated microbead product (Creon®). None of the formulations at the different doses given reliably resolved steatorrhea. Mean plus standard deviation of the different doses are shown[5,8,81].

the FDA (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf). These studies have been done well from a technical standpoint and used reliable methods for fecal collection and for analysis. The results are most often presented as the mean coefficient of fat absorption (CFA), which is calculated as [(fat intake - fat excretion)/fat intake] × 100 on a 72-h stool sample often collected in a controlled environment, plus the standard deviation. However, this presentation is of limited value to clinicians, as it does not provide definitive clinical data that would be useful in predicting clinical and symptom response, especially among patients with a previously unsatisfactory clinical response. For example, one would like to know the proportion of patients achieving a coefficient of fat absorption of at least 85%, as well as the median and range or 25%-75% values. Such data provide a clearer picture of what might be expected in clinical practice[42]. These data were requested from the manufacturers but not provided.

In some studies the patients may also not be representative. For example, Stern *et al*[80] included only patients who achieved at least 80% coefficient of fat absorption during a run-in phase on therapy, thus excluding the difficult to manage patients and improving the odds of an overall good outcome. In another study, approximately one-half of the subjects had minimal or no steatorrhea with placebo[4]. At least the data for the subgroup with significant steatorrhea was also provided separately in the outcome table[4]. Most trials have been relatively small because as they were powered only to detect a difference from placebo; however, the results may not extrapolate well to clinical practice. As shown in Figures 12 and 13[4,5,8,81] and Table 3, different formulations and lipase dosages have tended to provide similar results irrespective of the quantity of lipase administered. These results are consistent with the notion that only some of the lipase in the formulation was biologically available and overall

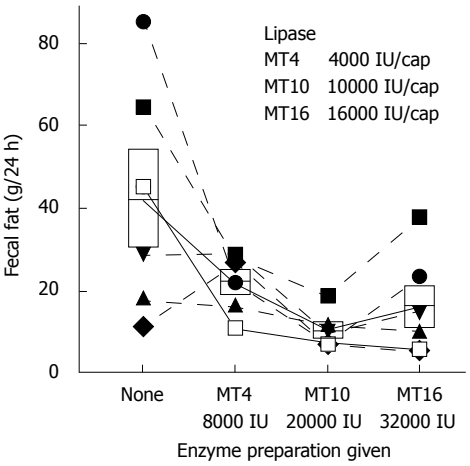

Figure 14 Effect of increasing the dosage of enteric coated microsphere preparation on fecal fat excretion is shown. Sorted by treatment groups and individual data for all subjects. Increasing the dosage from 8000 IU 4-fold (24000 to 128000 USP units) failed to show a clear dose response effect or to reliably resolve steatorrhea. The box shows the mean and standard deviation for each group. From[65] with permission.

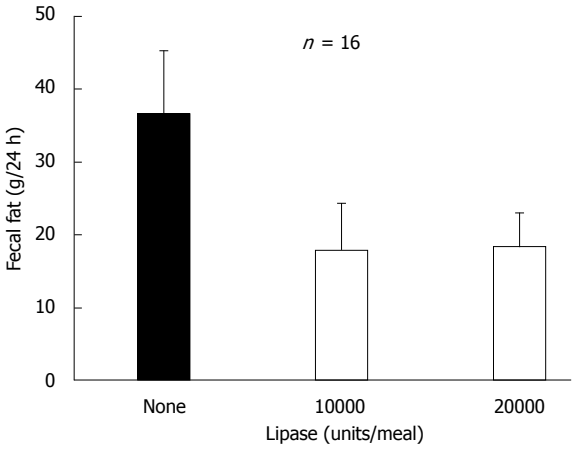

Figure 15 Effect of acid suppression with 60 mg of omeprazole on effectiveness of enzyme therapy with an enteric coated microsphere preparation (Pancrease®). Comparison of 2 dosing regimens 10000 (2 capsule of 5000 USP Pancrease®) or 20000 USP (4 capsule 5000 USP Pancrease®) lipase units per meal. The results were the same and neither resolved the steatorrhea[82].

was in excess of a threshold amount required to achieve the results reported. Importantly, these studies confirmed prior experience with enteric coated enzymes which also failed to show evidence of a dose response in terms of a reduction in steatorrhea[42,65,67,82] (Figures 7, 11, 14 and 15). Current products are priced in terms of dollars per units of enzyme (Table 3) such that the administration of more lipase than necessary serves only to increase cost to the patient without a corresponding increase in efficacy. A good example was a study that compared 7 capsules of Zenpep® 5000 (*i.e.*, 35000 USP units per day) a dose at which the authors expected "little or no effect on steatorrhea", with 7 capsules of Zenpep® 20000 (140000 USP units per day). The low and high doses produced similar outcomes (Figure 12)[4]. However, although the efficacy with high and low dose therapy did not differ, the cost of therapy per year was $11000 for high dose and $3000 for the equally effective low dose. These results confirmed that currently available products show (1) there is general lack of a dose-response effect; (2) increasing the dosage increases the cost more than the effectiveness; (3) a significant proportion of patients will still have clinically significant malabsorption despite enzyme therapy; and (4) a poor response to one dose generally signifies poor responsiveness to dose escalation.

One new preparation contains pancrelipase and sodium bicarbonate as a buffer to protect the enzymes and theoretically improve the pH in the small intestine (Pancrecarb®). It is called "highly buffered" although each capsule contains only 2.5 mEq of sodium bicarbonate. In clinical trials it was shown to be at best slightly better to not different from unbuffered capsules, and neither study achieved resolution of steatorrhea[83,84]. Currently, the FDA-approved Pertyze® is the only bicarbonate buffered pancreatic enzyme available. As noted above, studies of new concepts would probably be more efficiently initially evaluated using the ^{13}C-mixed triglyceride breath tests than through the use of expensive clinical trials.

Use of unprotected enzymes in the 21st century

An acid unprotected formulation of enzymes (Viokaze®) was recently FDA approved. While unprotected enzymes have limitations in relation to the relatively brief window in which the gastric pH is above 4, they may have a role in combination with enteric coated microbeads. In years past when *H. pylori*-associated atrophic gastritis was common, many adults had low acid secretion such that patients with pancreatic insufficiency often varied greatly in gastric secretory ability. In the modern era, *H. pylori* has become infrequent, and most adults exhibit normal acid secretion such that their intragastric pH falls to below 4 soon after eating and almost always within 60 min[54]. For these patients it is difficult to achieve or maintain an intragastric pH above 4 for a prolonged period using only antacids or antisecretory drugs. In the peptic ulcer era the goal of antacid or antisecretory therapy was to reduce acid output and thus the duodenal acid load. H_2-receptor antagonists typically reduce acid secretion by approximately 50%, which increases the average gastric pH for ulcer patients from approximately 1.4 to approximately 2, but increases the duodenal pH to above 4. Standard doses of proton pump inhibitors (*e.g.*, 20 mg of omeprazole) produce approximately a 90% reduction in acid secretion and an intragastric pH of 3 to 4[85]. A double dose (*e.g.*, 40 mg of omeprazole) provides 99% inhibition of acid secretion with narrow confidence intervals but will not reliably maintain the pH at 6 or above (which is the rationale for continuous infusion proton pump therapy in treatment of upper gastrointestinal ulcer bleeding)[85].

Studies of intragastric pH during meals have shown that the intragastric pH rapidly increases to the approximate pH of the meal, typically about pH 5, which stimulates the stomach to secrete acid maximally[54]. Initially, se-

creted acid is largely consumed by the buffering capacity of the meal such that average volume in the stomach remains relatively constant despite emptying. By 1 h, the intragastric pH falls to approximately 3, resulting in down-regulation of acid secretion allowing gastric emptying to exceed secretion such that the intragastric volume and the pH to continue to fall[86-91]. In normal subjects, one can expect the intragastric pH to fall below the threshold for lipase destruction between 30 min and one hour after eating. The longer the acid secretory rate is suppressed, the longer the lipase can remain active. In peptic ulcer disease, the recommendation was to administer antacids 1 and 3 h after meals in order to reconstitute the buffering capacity of the meal and achieve the maximum benefits for treatment of peptic ulcer disease. When used as an adjuvant to enzyme therapy, the goal is to maintain the pH above 4 or above for as long as possible in order to prevent inactivation of lipase.

pH is measured on a log scale such that each unit of change signifies a 10-fold change in acid concentration. Thus, a pH of 1 is equal to 100 mEq/L and a pH 6 equals 0.001 mEq/L. Parietal cells secrete acid at a high concentration (*e.g.,* 140-160 mEq/L); hence only a few active parietal cells secreting a small amount of concentrated acid can drop the pH below 4 and inactivate lipase[85]. Since high intragastric pH stimulates the stomach to secrete maximally, it is practically impossible to provide sufficient sodium bicarbonate or aluminum hydroxide to reliably maintain the intragastric pH above 5. However, the combination of an antisecretory drug to inhibit parietal secretion, coupled with an antacid to increase the pH and neutralize the small amount of acid secreted after inhibition of the majority of parietal cells, should be effective. Sodium bicarbonate is probably the ideal antacid as it is "natural," widely available in 325 mg (4 mEq) and 650 mg (8 mEq) tablets, and cheap. Although the ideal strategy remains to be determined experimentally, we recommend use of a proton pump inhibitor such as 40 mg of omeprazole daily along with 650 mg sodium bicarbonate tablets administered whenever unprotected enzymes are administered (*i.e.*, 1 tablet 2 or 3 times with the enzymes during the meal) and 1 and 2 h after meals. Current technology using the Smart Pill®[92] or Bravo®[93] to measure pH in the stomach and duodenum should rapidly identify the ideal timing and dosage of administration of the sodium bicarbonate.

Use of unprotected and enteric-coated enzymes in combination

Another approach to improve the results of enzyme therapy is to take advantage of the benefits of both unprotected and enteric coated formulations. Unprotected enzymes mix well with the meal and initially provide high duodenal lipase activity and fat digestion. However, depending on the acid secretory ability of the patient, when the gastric pH falls below 4, lipase will be inactivated providing a pattern of "effective early-ineffective late" therapy[32,33,51]. This pattern can be overcome by inhibiting acid secretion and using antacids to raise the pH to extend the duration of high pH gastric contents.

The pattern of effectiveness of enteric coated beads is one of "ineffective early - effective late". Combining the two approaches by starting therapy with unprotected enzymes followed by coated formulations would theoretically achieve a pattern of "effective early and effective late" and provide enzymes in parallel with gastric emptying of nutrients. We previously recommended this approach based on our experience[94]. The concept is supported and was given a firm physiologic basis by the exquisite studies by Gow *et al*[32] and Delchier *et al*[33] who used gastric and duodenal intubation to evaluate duodenal pH, enzyme and bile acid concentrations, and intraluminal digestion combined with fat balance studies. Meyer *et al*[37] also recommended the combination of unprotected and coated enzymes based on their elegant studies of emptying of enteric coated microbeads. To our knowledge no one has taken up the challenge of further investigating the combination approach, possibly because the recent focus has been on obtaining regulatory approval for new products rather than optimizing their effectiveness. More efficient use of available products would also require less enzyme and thus lower sales. The recent availability of an approved uncoated product (Viokaze) now makes testing the hypothesis possible.

Putting it all together

Based on perfusion studies and on theoretical grounds it has been suggested that 25000 to 50000 USP units of lipase should be administered per meal to achieve normal fat digestion and absorption[22]. As shown above, experience with pancreatic enzyme therapy with individual patients has shown that 18000 to 30000 USP lipase units per meal is probably the minimum needed for complete resolution of steatorrhea. Clinical trials with patients always trump laboratory experiments, and theoretical models and trials are needed to test and confirm hypotheses regarding most efficient use of enzymes. The one common feature of studies that has shown complete correction of steatorrhea is the presence of active lipase in the intestines for long periods, either because of the administration of unprotected enzymes or dissolution of enteric coated products in the stomach and their continued activity because the pH remained high[13,28,33]. The enteric coated product studied by Delchier *et al*[33] (Eurobiol 25000®) was very slow to dissolve after it reached the small intestine such that the amount of lipase measurable at the ligament of Treitz was similar to that following placebo. In contrast, those with high intragastric pH and rapid gastric emptying had high levels of intraduodenal lipase as well as intraduodenal absorption of triglycerides. Because a significant proportion of fat is emptied during the first 30 min of the meal, it is critical to provide exogenous lipase during that period. Potential approaches to solving this problem include: (1) the use of antacids and antisecretory drugs to prevent intragastric acidification; (2) administration of uncoated enzymes and possibly

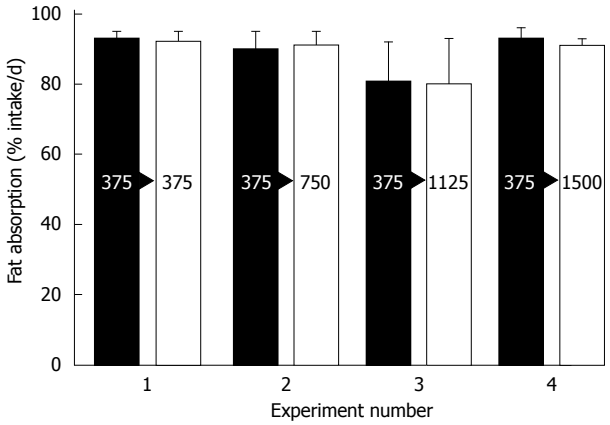

Figure 16 Data from 4 studies in children with cystic fibrosis comparing 375 USP lipase units/kg/meal to higher doses for the effect on steatorrhea. The results did not show a consistent effect on increasing the lipase dosage of an enteric coated preparation (Pancreaze®). Mean plus standard deviation are shown[79].

some sodium bicarbonate at the start of the meal; or (3) identify a strategy of emptying enteric coated products in the earliest portion of gastric emptying (for example, administer them before and during the meal). The dissolution characteristics of enteric coated products need further evaluation to examine when, where, how rapidly, and how completely the enzymes are released, and how these data relate to their clinical effectiveness.

Similarly, further studies are needed to address which changes in the timing of administration of pancreatic enzymes best coordinate pancreatic enzymes with emptying of gastric contents. For example, in three recent reviews the recommendations vary from 50% at the beginning of the meal and 50% at mid-meal[95], to during or immediately following the meal[96] and 25% with the first bite, 50% during the meal and 25% with the last bite[97]. From the available data and the data showing that a considerable amount of fat is emptied in the first hour, it is prudent when using enteric coated microbeads to start therapy just before the meal so that some microbeads are emptied during the first hour, then distribute the remaining enzymes throughout the meal. Those with hyperacidity may also benefit from adjuvant antisecretory therapy to reduce the duodenal acid load. However, it may not be possible to find an ideal schedule if one is restricted to using only enteric coated microbead therapy. Below we will discuss the available experience with currently approved therapies.

It has been known since the earliest days of pancreatic enzyme therapy that the patients who reliably experience good response are those with limited or no acid secretion. While the research focus has long been on duodenal lipase levels[22] one must now also consider how much and whether intragastric lipolysis due to the exogenous lipase contributes to the outcome. It should be clear that we have moved beyond the current "better than placebo" era of research aimed at obtaining regulatory approval for commercial products, and now need to focus on understanding how to reliably provide therapy and how to best use the available products.

More is not better using modern formulations

As a general rule for both unprotected and enteric-coated beads, the effect on steatorrhea is not directly related to the amount of lipase administered (namely, that after a threshold response, any further increase in the amount of enzyme given provides little or no additional benefit). This phenomenon has resulted in misinterpretation of many studies. For example, consider an experiment where the same dose of lipase is given using two different formulations (*e.g.*, 10 capsules are compared to 1 of another) with both formulations providing the same quantity of lipase. If both produce the same reduction in steatorrhea, the investigators would be tempted to conclude that one could use the formulations interchangeably, provided that the same quantity of lipase was administered. However, if they had included controls with one-half and with double the quantity of enzyme, they would likely have achieved the same result. This trap was revealed by studies examining whether there was a lipase dose - fecal fat responses (*e.g.*, Figures 12-16)[4,5,8,65,79,81,82]. For example, administration of 8000, 20000 or 32000 units of lipase using three different preparations of an enteric-coated commercial product produced no consistent change in fat malabsorption[65] (Figure 14). Figures 12, 13, 15, and 16 show more recent examples with a variety of enteric-coated products[4,5,8,81,82,98]. Figure 16 is especially revealing: in this study 4 subjects per group (children with cystic fibrosis) received therapy with 375 units of lipase/kg per day and then were given a different dose of 375, 750, 1125, or 1500 units/kg per day[79]. Clearly, the results with increasing to higher doses were almost identical.

Marketing strategies of companies selling pancreatic enzymes include attempts to link the amount of lipase required to fat intake and suggest that providers or patients increase the dosage in response to an unsatisfactory clinical response. Except for the low dosage products (which are priced about twice as high), enteric-coated pancreatic enzymes are currently priced between $2 and $4 per 10000 lipase units (Table 3). The lack of studies showing "more is better" and lack of head-to-head comparisons makes choice of therapy a matter of judgment.

Adding microspheres to food or putting them down feeding tubes

Enteric coated products to be taken orally are designed to dissociate when the pH is 5.5 or greater. The Cystic Fibrosis Foundation recommendations are consistent with the current package inserts: for infants and patients that are unable to swallow, recommended administration is to open the capsules and sprinkle its contents onto soft food mixtures with pH of 4.5 or less (*e.g.*, applesauce). The recommendation is based on theory rather than analysis of interaction of the enteric coating with complex formulations such as food. Sackman *et al*[99]. addressed the issue of mixing enteric-coated pancreatic enzymes with various food contents at various pH. They incubated en-

Table 5 Data needed to understand how to use new enzyme formulations

Results of all studies should not be withheld but should be published and/or placed on Clintrials.gov within 1 yr of completion
Trial data should provide the primary efficacy endpoint (*e.g.*, coefficient of fat absorption) as mean, standard deviation, median, range, and proportion with coefficient of fat absorption > 90% as well as proportion with coefficient of fat absorption < 85%
Gastric emptying of enteric coated pellets studied for all products are needed and the data should be published and/or placed on Clintrials.gov within 1 yr of completion
Kinetics of dissolution of enteric-coated microbeads in intestinal fluid or simulated intestinal fluid are needed and should include data pH's starting at approximately pH 5 through 7 at increments (*e.g.*, approximately 0.2 pH units)

Table 6 Recommended clinical trials

Head to head comparisons of different formulations within a product line as well as between commercial products
Comparative trials using different patterns of administration in relation to meals of enteric coated products (*e.g.*, before and during)
Studies combining unprotected and enteric coated preparations
Studies of unprotected preparations combined with maintenance of the intragastric pH constantly above 4
Initial pilot studies using ^{13}C-mixed triglyceride breath testing to test proof of concept may be the most efficient means of identifying which studies to test in human clinical trials

teric coated enzymes in saline, various food products with pH ranging from 5.6 to 6.5, and applesauce with pH of 3.4 and measured dissolution time as a surrogate for the integrity of the enteric-coating. Trypsin activity was used as a surrogate for lipase release. Among the foods tested, only applesauce reduced the integrity of the enteric-coating[99]. That study was conducted in 1982 with an older formulation but showed that theory is always subject to confirmation by experimentation. Studies with newer formulations are needed. Until that time it is likely that mixing with any food would be safe, although applesauce should probably be avoided. Shlieout *et al*[100] in an *in vitro* study mixed Creon 12000® in various baby foods with pH 4.5 or less to study use of pancreatic enzyme activity after passing it through various G-tubes. They found that the 16F Kimberly-Clark MIC-KEY tube was the smallest diameter tube that allowed passage of all food mixtures without clogging. Using tubes from other manufactures, they found that only 18F and larger tubes were able to pass all food content without clogging. All preparations retained 89.9% to 96.9% of the expected lipase activity. Nicolo *et al*[101] published 4 cases of patients dependent on enteric feeding and pancreatic enzyme supplementations. They reported that mixing pancreatic enzyme in all vehicles, including saline, applesauce, and fruit juices resulted in clogging of the tube; however, mixing the pancreatic enzyme in 8.4% solution of bicarbonate was effective. Interestingly, the combined use of pancreatic enzymes and bicarbonate is a common method used to unclog feeding tubes[102].

Recommended therapy

For the average patient, we recommend three, approximately 10000 USP units of lipase containing enteric coated microbead capsules/tablets per meal and one with snacks (*e.g.*, approximately 40000 USP units for an adult). The first dose is given before meals and the others during the meal. Following an unsatisfactory response one might consider adding approximately 20000 units lipase during meals. There are no data that increasing the dosage further increases effectiveness and is likely "beating a dead horse". Instead one should consider changing to a product with different characteristics (*e.g.*, from a microsphere to a minitablet), adding a unprotected enzyme product at the start of the meal, and/or adjuvant therapy with an PPI and/or sodium bicarbonate. As noted previously, one-third to more than one-half of patients will require therapy to be individualized. One should also consider the possibility of a second cause of malabsorption such as celiac disease or bacterial overgrowth. Treatment success should be assessed clinically and whenever available by an estimate of fat absorption. Longer term success should also be monitored in terms of maintenance of normal levels of fat soluble vitamins.

CONCLUSION

Hopefully, the current era of studies primarily targeted to obtaining FDA approval and marketing new products will soon transition into an era focusing on overcoming the remaining barriers that have limited the overall effectiveness of pancreatic enzyme therapy. In many ways we have not progressed beyond what was known in the 1980's. There are many options that potentially would improve current therapy and we have outlined a number of possibilities (Tables 5 and 6). A number of options need further testing, including the effects of combining unprotected enzymes (given with the first few bites and/or with sodium bicarbonate to buffer residual acid) in combination with enteric coated enzymes given throughout the meal. Hopefully comparative studies and studies of gastric emptying and dissolution of each formulation during normal meals will be done, and that results of those studies will be published in a timely manner.

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