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Use of a Mutilumen Catheter to Assess the Bioavailability of an Enteric-Coated High-Buffered Pancrelipase Formulation in Patients with Exocrine Pancreatic Insufficiency

Ahsan N. Rizwan[1], Ryan Criste[1], Noelia Nebot[1], Kristina K. Wolf[1], Kim L. R. Brouwer[1] and Lisa M. Gangarosa[2]*

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7569, USA
[2]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599-7080, USA

Abstract

Treatment of exocrine pancreatic insufficiency (EPI) secondary to conditions including cystic fibrosis or chronic pancreatitis requires exogenous supplementation with a specially formulated pancreatic enzyme product (PEP). The FDA has mandated that the intestinal bioavailability of these preparations be evaluated *in vivo* in patients.

This pilot clinical study examined the feasibility of using a multi-lumen catheter with an occluding balloon to measure changes in intraduodenal enzyme concentrations following oral administration of a PEP.

In this two arm cross-over study, patients with mild-severe EPI were administered enteric coated (EC) high-buffered pancrelipase or placebo capsules with a liquid Lundh meal. Gastric and duodenal samples were aspirated at 15-minute intervals over 3 hours in each treatment arm. The concentrations of three pancreatic enzymes (lipase, amylase, and protease) were measured in the collected fluids. The maximum concentration (C_{max}), and area under the duodenal enzyme concentration vs. time profile (AUC) were determined.

Comparison of enzyme concentrations between placebo and treatment phases demonstrated appreciable increases in all three enzymes in the subject with cystic fibrosis (CF+), but only a modest increase in the subject with mild-to-moderate EPI (CF-). During the EC-high-buffered pancrelipase+meal phase, the fold increase in the C_{max} of lipase, amylase, and protease concentrations compared to the placebo+meal phase in subject CF- were 0.96, 1.65, and 1.64, respectively. In subject CF+, who had severe pancreatic enzyme insufficiency, the fold increase in the AUC of lipase, amylase and protease concentrations compared to the placebo+ meal phase was 66.1, 15.9, and 651, respectively. Time to peak concentration occurred earlier during the active treatment phase. In both subjects and both treatments a peak duodenal pH of 8 was measured.

The catheter employed in this study can be used to determine bioavailability of PEPs in severe EPI in a single-day pretreatment vs. post treatment setting (NCT00744250).

Keywords: Exocrine pancreatic insufficiency; Cystic fibrosis; Enteric coated high buffered pancrelipase; Intraduodenal; Aspiration; Catheter

Abbreviations: AUC: Area Under the Duodenal Enzyme Concentration vs. Time Profile; CLIA: Clinical Laboratory Improvement Amendments; CTRC: Clinical and Translational Research Center; EC: enteric coated; EPI: exocrine pancreatic insufficiency; FDA: Food and Drug Administration; IRB: Institutional Review Board; NDA: New Drug Appliation; PEP: Pancreatic Enzyme Products; USP: United States Pharmacopeia

Introduction

Pancreatic enzyme products (PEPs) have been in use for decades to treat patients with deficient production of pancreatic digestive enzymes, a condition known as exocrine pancreatic insufficiency (EPI). Patients suffering from EPI are unable to produce sufficient pancreatic enzymes of their own to aid digestion. In adults with EPI secondary to acute/chronic pancreatitis or pancreatic cancer, this leads to steatorrhea and weight-loss. In children with EPI secondary to cystic fibrosis or Shwachman-Diamond Syndrome, this condition can also result in malabsorption with subsequent growth and development-related disorders [1].

Since most PEPs are specially formulated from porcine pancreas, considerable differences in enzyme activity are to be expected from different manufacturers and from batch to batch. The development of fibrosing colonopathy has been linked to administration of high potency (>20,000 USP units of lipase/capsule) and high dose pancreatic enzyme replacement therapy over time [2,3]. Substitution between branded and generic PEPs resulted in therapeutic failure [4,5]. The enzymes contained in these products are prone to inactivation if the gastrointestinal pH is not within the optimum pH range (e.g. pancreatic lipase is irreversibly inactivated in the acidic pH of the stomach). In one instance, failure of the enteric coating resulted in withdrawal of a product from the market [6]. Deficient bicarbonate secretion in patients with pancreatic insufficiency results in insufficient neutralization of bile acids in the upper intestine, which can increase the risk of enzyme inactivation in the duodenum if the PEP is formulated without a buffering agent. PEPs from different manufacturers are, therefore, not pharmaceutical equivalents, and inappropriate substitution in the absence of bioavailability studies may lead to overdosing, which can have serious consequences resulting in

hyperuricosuria, hyperuricemia, and colonic strictures [7]. Since PEPs were originally marketed before the Federal Food, Drug, and Cosmetic Act of 1938 was passed, they had been exempt from a formal FDA review and approval process. However, in 2004, the FDA required a New Drug Application (NDA) for all PEPs. In April 2006, the FDA issued Guidance for Industry on NDA requirements for PEPs. One of the requirements was determination of bioactivity/bioavailability of the exogenously administered enzymes at the site of action (i.e., the gastrointestinal tract) from aspirates collected from the stomach and duodenum.

The aim of this study was to assess the feasibility of using a specially designed multi-lumen catheter to collect gastric and duodenal samples from patients with EPI to determine the bioavailability of an enteric coated (EC) high-buffered pancrelipase (Pancrecarb˚). Previously, we reported the use of a multi-lumen catheter (CHOL-ect) for several applications: evaluation of drug absorption following administration in different regions of the gastrointestinal tract; measurement of the effect of pancreatico-biliary secretions and gastrointestinal transit time on drug absorption and pharmacokinetics; determination of biliary clearance of drugs in humans; and assessment of the influence of hepatic transporter modulation on hepatic exposure of drugs in humans [8-14]. The use of catheters to determine the fate of orally ingested enzymes has been described in the literature. [15] compared an EC-PEP to a conventional PEP vs. placebo using double lumen oro-gastric and oro-duodenal tubes; a continuous perfusion technique was employed to sample over 4 hours and 3 consecutive days (one day for each treatment) in six adult patients with pancreatic insufficiency [15]. In another study, cumulative postprandial enzyme levels were assessed in healthy volunteers and subjects with EPI receiving either placebo or an EC-PEP [16]. Samples were obtained in a similar fashion utilizing a 5-lumen catheter.

The methodology used in the present study was designed to evaluate whether meaningful increases in pancreatic enzymes could be achieved after administration of 5 capsules of an EC-buffered PEP (containing 16,000 USP Units of lipase per capsule). With the present modified catheter, we were able to perform the catheter placement in a relatively short period of time so that the two treatment arms, placebo and active treatment, could be conducted on the same study day. Data from two different subjects, one with mild-to-moderate and one with severe EPI, were compared in this study.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill. All the patients gave their informed consent. The registration number for this study on ClinicalTrials.gov is NCT00744250.

Study drug

The study drug was formulated as delayed-release microspheres (particle size range of 0.6-1.5 mm) filled in clear gelatin capsules incorporating buffered (2.5 mEq of bicarbonate per capsule) pancreatic enzymes (lipase, amylase, and protease) isolated from concentrated porcine pancreatic glands. The drug (now named Pertzye) was first marketed in the USA in 1995 by Digestive Care, Inc as Pancrecarb˚ (16,000 USP units of lipase per capsule). The enzyme-containing microspheres are coated with a pH-sensitive polymer coating to provide protection against gastric inactivation of the buffer-stabilized enzymes during gastric passage. Five EC-high-buffered pancrelipase capsules containing lipase (16,000 USP units), amylase (52,000 USP units) and protease (52,000 USP units) were administered in this study

(Table 1). Capsules were filled to 100% lipase with no overfill. Placebo consisted of white opaque gelatin capsules filled with EC microspheres. Placebo capsules contained all the excipients including the bicarbonate buffer minus the active drug substance, pancrelipase.

Test meal and administration

The study drug and placebo capsules were administered with a standardized test meal known as the Lundh meal [17-19]. The liquid Lundh meal is designed to simulate a fed state and to stimulate pancreatic secretions. The Lundh meal was prepared by the research kitchen at the UNC Clinical and Translational Research Center (CTRC) for administration with the EC-high-buffered pancrelipase and placebo capsules. It was composed of 26g skim milk powder, 40g dextrose, and 19g corn oil. Distilled water (290 mL) was added to a final volume of ~360ml. The preparation was mixed thoroughly prior to administration. It was given to the subject in a cup and the subject was required to drink the whole preparation via a straw within 10 minutes.

Sample collection device (the CHOL-ect multi-lumen catheter)

The CHOL-ect multi-lumen catheter (Figures 2A and 2B) was used for gastric and duodenal aspiration. This customized polyvinyl chloride (PVC) catheter was designed by Ghibellini, Johnson, Heizer, Brouwer and co-workers in collaboration with Dentsleeve International Ltd (Mississauga, Ontario, Canada). The catheter, currently manufactured by Mui Scientific, Inc (Mississauga, Ontario, Canada), has an outer diameter of 7.1 mm for the first 100 cm, and 4.6 mm for the remaining 28 cm. An inflatable non-latex balloon is located at the tip with radio-opaque marker rings at three positions along the length of the catheter. This inflatable balloon is used to occlude the duodenal lumen to increase collection efficiency. The lumen of the catheter consists of eight channels for: 1) duodenal aspiration, 2) teflon-coated guidewire insertion, 3) duodenal vacuum relief, 4) stomach vacuum relief, 5) proximal duodenal saline flush, 6) distal duodenal saline flush, 7) balloon inflation, and 8) gastric aspiration [20]. The large number and the distribution of aspiration/perfusion ports along the catheter add to the versatility of the device for different applications. Prior to use, the catheters were inspected visually for any damage, tested to make sure all channels were clear and autoclaved utilizing ethylene oxide gas autoclave technique [21]. For positioning, a teflon coated guide-wire was inserted into lumen #2.

Study procedure

This was an open label, cross over, two arm (pretreatment versus post-treatment) single center study. The study involved one out-patient visit for screening, and one in-patient visit for the aspiration procedure.

Screening visit: Potential subjects were screened if they required daily exogenous enzyme supplementation with commercially available pancreatic enzymes, were ≥ 18 years of age, were a male or non-pregnant female, confirmed the ability to swallow large capsules, and had no acute medical conditions in the last 3 months. Informed consent was obtained. During screening, subjects underwent a medical history assessment, physical exam, and clinical laboratory testing.

		Theoretical concentration with a dose of 5 capsules and 350 mL meal volume
Lipase	16,000 USP Units	229 USP Units/mL
Amylase	52,000 USP Units	743 USP Units/mL
Protease	52,000 USP Units	743 USP Units/mL

USP-United States Pharmacopeia; enzymes are of porcine origin

Table 1: Labeled potency of pancreatic enzymes in EC high-buffered pancrelipase capsules.

A spot fecal elastase 1 test from a stool sample was used to confirm pancreatic enzyme insufficiency in patients [22]. Subjects were selected for the study only if the spot fecal elastase 1 was <200 µg/g at the time of screening [23-25].

Study visit: Eligible subjects began the study phase within one month of screening. Subjects arrived at the CTRC the evening before the study. Upon admission, the subject underwent assessment of vital signs and placement of an IV drip (0.9% normal saline solution at 125mL/hr for hydration). Subjects were asked to fast after midnight. The next morning, fluoroscopic assisted placement of the catheter was performed by the team, as detailed previously [8-14]. The catheter was placed orally and the distal tip positioned in the distal duodenum. An oral anesthetic (benzocaine) was administered if requested. Following successful placement, the tube was taped to the outside of the cheek to prevent further movement of the tube down the intestine.

Aspiration procedure: Following successful catheter placement, the subject was taken to his/her room and rested in a comfortable chair in an upright position. The study was divided into two phases, a placebo+meal phase and an active treatment+meal phase, with a one-hour rest in between. In each phase, prior to administration of the capsules and liquid diet, aspiration of baseline gastric and duodenal secretions was attempted. Subsequently, subjects were asked to swallow 5 capsules administered orally along with the liquid meal (Lundh diet) within 10 min. Gastric and duodenal fluids were aspirated continuously over 180 min at 15-min intervals via the catheter. The balloon was inflated at 45 min. After the first 180 minute phase, the balloon was deflated and the subject had a 60-minute rest period. The internal lumen of the tube was cleaned with a saline flush. After both phases were complete, the balloon was deflated and the catheter was removed. The subject was permitted to resume his/her normal medications and discharged after a one-hour observation period.

Sample processing and enzyme assays: The volume of the sample that was aspirated during each collection interval was recorded. All aspiration samples were kept on ice during collection. Samples were aliquoted, frozen, and shipped overnight on dry ice for analysis. Samples were tested for lipase, amylase, and protease activities. All enzyme activity assays were performed in the CLIA (Clinical Laboratory Improvement Amendments) certified Gastroenterology Laboratory at Nemours Children's Hospital, Wilmington, DE. Enzyme concentration was reported as activity in USP units/mL of sample. The pH and protein content of the aspirates were determined and enzyme fingerprinting (data not shown) also was performed to confirm the presence of the exogenous source of enzymes.

Data analysis: The maximum enzyme concentration in each phase was determined by visual inspection of the data. The area under the duodenal enzyme concentration vs. time profile (AUC) through the last time point was determined by the linear trapezoidal method in WinNonlin version 5.0 (Pharsight Corporation, Palo Alto, CA, USA).
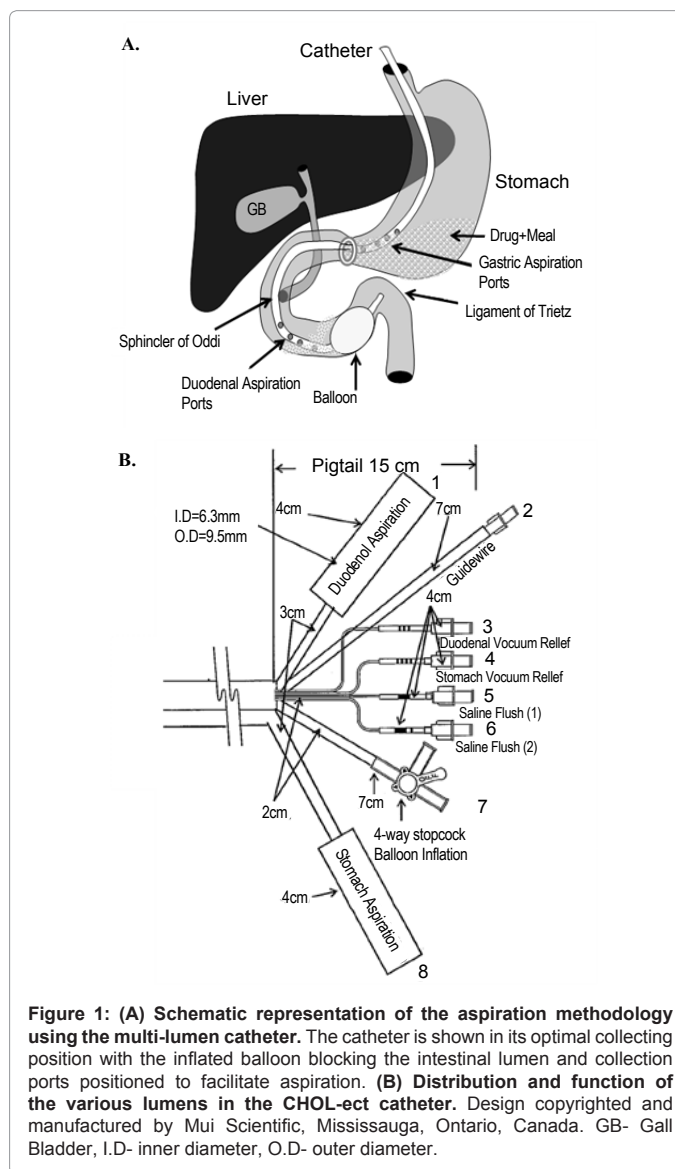
Aspiration procedure

Data from two subjects, a patient with cystic fibrosis and a patient without cystic fibrosis, referred to henceforth as subjects CF+ and CF-, respectively, are presented in this study. Subject characteristics and fecal elastase 1 levels are shown in Table 2. Baseline gastric secretion prior to meal administration was acidic with a pH of 1.9 and 2.5 for subjects CF- and CF+, respectively. In both subjects, baseline duodenal samples could not be obtained at the start of the study (placebo+meal phase), presumably because of the overnight fasting. The pH of duodenal contents was maintained at values >6 for both patients during both EC-

Patient	Age	Sex	Race	Spot Fecal Elastase 1 (µg/g stool)
CF-	57	F	Caucasian	190
CF+	30	M	Caucasian	<15

CF- indicates subject did not have cystic fibrosis and had mild-to-moderate EPI; CF+ indicates subject had cystic fibrosis and severe EPI; F-female, M-male; µ-micro, g-gram

Table 2: Subject Demographics.

Figure 1: (A) Schematic representation of the aspiration methodology using the multi-lumen catheter. The catheter is shown in its optimal collecting position with the inflated balloon blocking the intestinal lumen and collection ports positioned to facilitate aspiration. **(B) Distribution and function of the various lumens in the CHOL-ect catheter.** Design copyrighted and manufactured by Mui Scientific, Mississauga, Ontario, Canada. GB- Gall Bladder, I.D- inner diameter, O.D- outer diameter.

high-buffered pancrelipase+meal and placebo+meal phases (Figure 2 and 3). Distinct spikes in duodenal pH were observed in both placebo and treatment phases.

The volume of the Lundh meal administered was approximately 360mL. In subject CF- the total volume (duodenal+gastric) collected was equal to or greater than the volume of the liquid meal in the placebo phase. In the placebo phase 443.5 mL of liquid was recovered; 359 mL was recovered in the active treatment phase. The larger total volume collected may reflect dilution with gastric/pancreato-biliary secretions and saliva. In the CF+ subject, 262 mL of liquid was recovered in the placebo phase and 246 mL was recovered in the active treatment phase.

Enzyme concentrations

The enzyme concentrations and pH at each time point of collection for the two subjects in the two treatment arms (placebo+meal and EC-high-buffered pancrelipase+meal) are shown in Figures 2 and 3,

respectively. The maximum duodenal enzyme concentration (C_{max}) and the area under the duodenal enzyme concentration vs. time curve (AUC) for each enzyme in each of the treatment arms are reported in Table 3. While only a moderate increase was observed in amylase and protease for subject CF- following active treatment (Figure 2), a
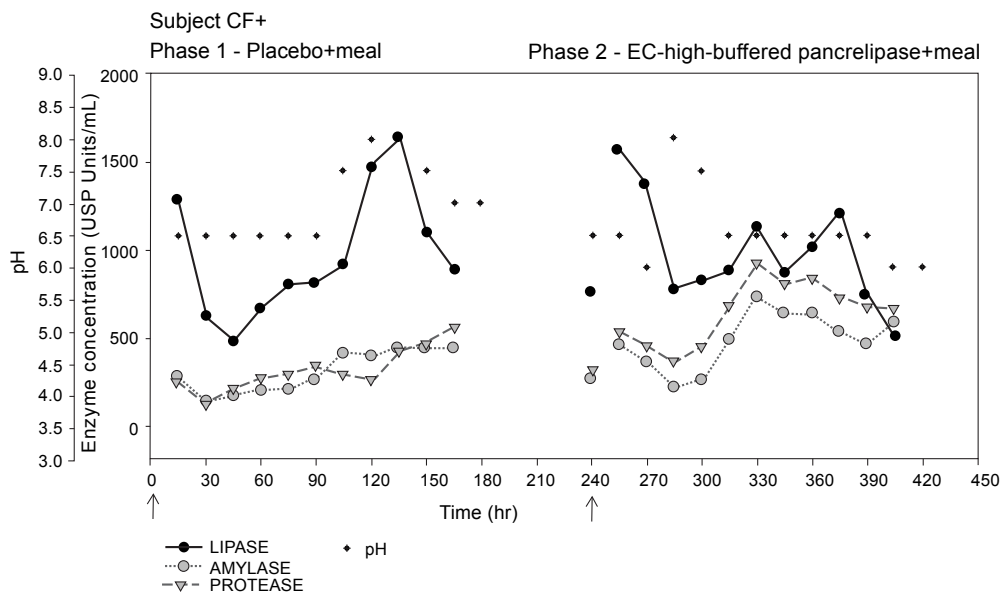

Figure 2: Duodenal enzyme concentrations and pHs in subject CF-. In Phase I (placebo+meal), the duodenal aspirate contained significant concentrations of all enzymes and the pH was increased due to the bicarbonate buffer content of the Placebo formulation. A steady increase in amylase and protease concentrations was observed with time. The pH was between 6.0 and 7.5 throughout the measurement interval. After administration of pancreatic enzymes in Phase II (EC-high-buffered pancrelipase+meal), the peak concentrations of protease and amylase were observed at 90 minutes post-dose (at 330 min in Phase II) and coincided with the peak pH of 7.5. Lipase concentration was variable, with no specific trend in relation to the pH. Arrows indicate time when all meal and study drug had been ingested and sample collection was started. Baseline concentrations are plotted at 240 min for Phase 2.
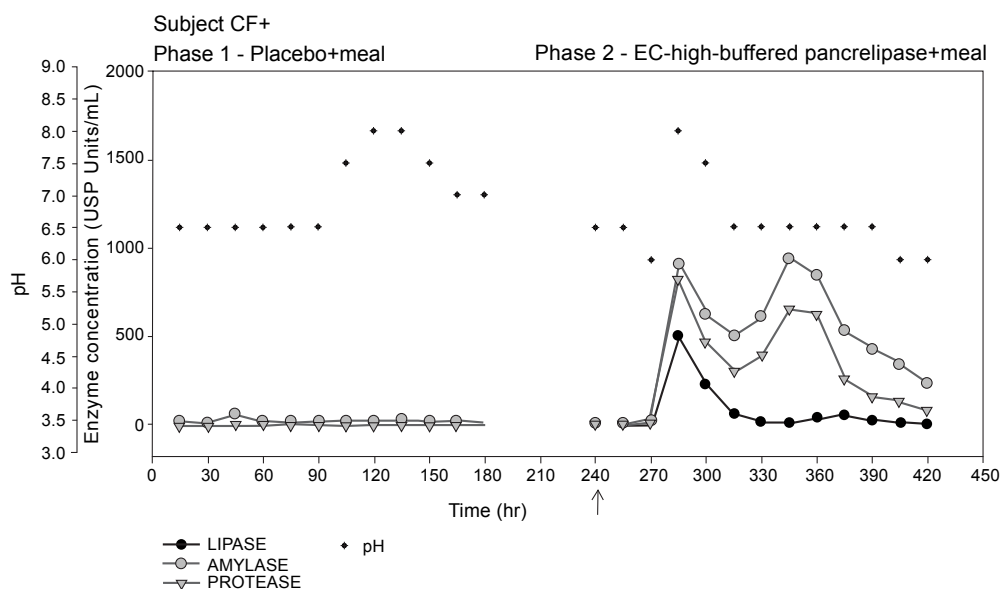

Figure 3: Duodenal enzyme concentrations and pHs in subject CF+. In Phase I (placebo+meal), the concentration of lipase and protease in the duodenal fluid were negligible, and there was a small amylase peak 45 min post-dose. The pH was 6.5 at onset, and increased to a maximum of 8.0 and then fell to a value of 7.0 due to the bicarbonate buffer content of the Placebo formulation. After administering pancreatic enzymes in Phase II (EC high-buffered pancrelipase+meal), lipase concentrations peaked at 45 min post-dose. Two peaks were observed for amylase and protease at 45 and 105 minutes post-dose. The pH increased from 6.5 at baseline to 8.0 at the first peak release of enzymes. Given the negligible background enzyme concentrations, this suggested both release of pancreatic enzymes as well as the bicarbonate buffer from the formulation in Phase II. Arrows indicate time when all meal and study drug had been ingested and sample collection was started. Baseline concentrations are plotted at 240min for Phase 2.

Enzyme	ID	EC-high-buffered pancrelipase			Placebo			EC-high-buffered pancrelipase/Placebo ratio	
		C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C_{max}	AUC
		USP Units/mL	min	USP Units*hr/mL	USP Units/mL		USP Units*hr/mL	min	
Lipase	CF-	1562	15	2737	1629	135	2538	0.96	1.08
	CF+	499	45	229	7.55	165	8.16	66.1	28.1
Amylase	CF-	735	90	1308	446	135	803	1.65	1.63
	CF+	942	105	1470	59.3	45	62.4	15.9	23.5
Protease	CF-	919	90	1736	559	165	809	1.64	2.15
	CF+	827	45	954	1.27	105	3.10	651	308

Ratios of peak enzyme concentration and AUCs, active treatment compared to placebo, are shown. C_{max}-peak enzyme concentration; AUC_{last}- area under the duodenal enzyme concentration vs. time curve through the last measurable time point, T_{max}- time to C_{max}.

Table 3: Comparison of duodenal enzyme concentrations.

substantial increase in all three enzymes was observed in subject CF+ (Figure 3).

During the EC-high-buffered pancrelipase+meal phase, the fold increase in the AUC of lipase, amylase and protease concentrations compared to the placebo + meal phase in subject CF- was 1.08, 1.63 and 2.15, respectively (Table 3). In subject CF+, who had severe pancreatic enzyme insufficiency, the fold increase in the AUC of lipase, amylase and protease concentrations compared to the placebo+ meal phase was 8, 24 and 308, respectively (Table 3).

Discussion

In the present study, we have demonstrated the feasibility of using a specially designed eight-lumen PVC catheter to assess intraduodenal pancreatic enzyme concentrations following exogenous enzyme supplementation with an EC high-buffered pancrelipase formulation. This is an important objective since the FDA now requires manufacturers to demonstrate adequate bioavailability of pancreatic enzymes from a given formulation. This requirement will aid in developing formulations with improved bioavailability. Also, knowledge of the in vivo bioavailability will ensure that appropriate doses are administered to manage EPI.

Subject with mild-to-moderate pancreatic enzyme insufficiency

Patient CF- had relatively high pancreatic enzyme concentrations in the placebo+meal phase indicating good exocrine pancreatic function. Hence, the subject may have had only mild-to-moderate EPI. Following administration of the EC-high-buffered pancrelipase+meal, an increase of approximately 2-fold in amylase and protease concentrations was observed, while almost no increase in lipase was evident based on AUC comparisons. It is difficult to hypothesize why an additive effect was not observed in enzyme concentrations after enzyme supplementation in subject CF- (Figure 2). One possible explanation may be found in comparing the temporal changes of enzyme concentrations between the two phases. Looking at the enzyme concentration vs. time profiles for subject CF- in Figure 2, a steady rise in the concentrations of amylase and protease was evident during the placebo+meal phase. The rise to peak was markedly different in the pancrelipase+meal phase. In the active treatment phase, the peak concentrations of amylase and protease occurred at 90 min, and then dropped off, representing drug release and decay. In the placebo phase, the peak enzyme concentrations occurred at the end of the profile possibly representing steadily rising exocrine pancreatic secretion in response to the meal (see T_{max} values in Table 3).

Subject with severe pancreatic enzyme insufficiency

For subject CF+ with severe exocrine pancreatic insufficiency, the results and interpretation of the data are more straight-forward and attributable to the treatment. In the placebo phase, subject CF- had extremely low levels of amylase, lipase and protease, even upon stimulation with the meal. Because of these low background levels, the differences between the two treatments (placebo+meal and EC-high-buffered pancrelipase+meal) could be observed very clearly (Figure 3). These results suggest that patients selected for intestinal bioavailability studies to assess PEPs could be stratified based on the degree of pancreatic insufficiency, and that severely deficient sub-populations should be analyzed separately. Patients with severe EPI are at the greatest risk from overdosing because of the high doses they require. Studies to demonstrate bioavailability of the PEPs in patients with cystic fibrosis would be clinically relevant. For patients with less severely compromised pancreatic function, an assay that could differentiate endogenous from exogenous pancreatic enzymes would be helpful in order to eliminate the background of endogenous pancreatic enzymes in these patients. In the present study, although we were able to confirm the presence of exogenous porcine enzymes through fingerprinting by protein SDS gel electrophoresis (data not shown), it was not possible to make a quantitative assessment of exogenously administered pancreatic enzymes only; thus, total enzymes were quantified.

Physiological sources of variability

Physiological factors such as the rate of gastric emptying, gastrointestinal pH, and gastrointestinal motility affect study outcome and increase intersubject variability. We excluded subjects with a recent history of gastrointestinal surgery. Subjects also were asked to refrain from taking any medications that might affect gastrointestinal motility prior to the study. It is also possible that some subjects may fail to maintain duodenal pH above the pH range required for dissolution of the EC microspheres. This is especially true for subjects with cystic fibrosis where bicarbonate secretion also is impaired. Bicarbonate secretion by the pancreas helps to neutralize the acidic contents that are emptied from the stomach. Pancrecarb* (Pertzye) is a preparation that contains 2.5 mEq bicarbonate per capsule (high-buffer formulation) in order to ensure that the enzymes released from the microspheres remain highly active in a buffered microenvironment.

Furthermore, EPI itself is difficult to diagnose and characterize in terms of mild, moderate, or severe insufficiency. Most tests of pancreatic function are only accurate in advanced disease [24]. The normal pancreas secrete 1-2 L of water, bicarbonate, digestive enzymes and other proteins and minerals per day under complex regulatory mechanisms [26]. Based on the underlying cause of pancreatic

insufficiency, the levels of these secretions will vary considerably from one individual to another. It also has been reported that patients may be deficient in only some enzymes and not others [24].

Utility of the CHOL-ect catheter

In the present study, the CHOL-ect catheter was used to measure the *in vivo* dissolution and release of lipase, amylase and protease enzymes from the EC-high-buffered pancrelipase in two subjects at two extremes of pancreatic insufficiency. The Lundh diet was chosen as the test meal because it is a reliable and standard method to stimulate both exocrine and endocrine pancreatic secretions. The use of this technique to assess the bioavailability of pancreatic enzyme preparations has several advantages. Most intestinal perfusion studies require several days for completion, with multiple catheter placements; in some studies, the catheter remains in position over several days. In contrast, the CHOL-ect catheter can be positioned on the day of the study, and two arms of the study (e.g. placebo vs. treatment) can be completed on the same day in the same subject. This greatly reduces subject discomfort and improves safety. Due to the large number of lumens in the CHOL-ect catheter, multiple catheters (e.g. nasogastric) do not have to be inserted and gastric and duodenal samples can be collected via the same catheter. Using manual suction by catheter tip syringes, sufficient volumes of both gastric and duodenal fluids can be aspirated. The presence of lumens, through which vacuum relief could be provided by injecting air using a 5 mL syringe, aided sample collection and also relieved patient discomfort if there was build-up of gas within the gastrointestinal lumen. During the rest period between treatment phases, the lumens can be cleaned using normal saline. Deflation of the balloon during the rest period also ensures that any remaining drug/meal from the first phase is cleared from the duodenum so that it does not interfere with measurements during the second phase.

Conclusion

This pilot study describes a novel methodology to accurately assess the *in vivo* intestinal bioavailability of pancreatic enzyme preparations. The study may be conducted in a crossover design with two treatment arms (placebo+meal and active treatment+meal) in order to minimize subject discomfort and reduce variability. The CHOL-ect multi-lumen catheter with an occluding balloon is amenable to the efficient collection of gastric and duodenal samples to assess changes in intraduodenal enzyme concentrations following oral administration of pancreatic enzyme preparations. With the use of an appropriate number of age and sex matched subjects to further reduce variability we believe that the methodology discussed here is an appropriate way to assess the bioavailability of PEPs in humans.

Acknowledgements

Statement of Interests

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