Review

Rational Prescribing of Pancreatic Enzymes for Patients with Pancreatic Cancer

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Rational Prescribing of Pancreatic Enzymes for Patients with Pancreatic Cancer

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Abstract: Most patients with pancreatic cancer at some point present with symptoms related to exocrine pancreatic insufficiency (EPI). These include diarrhea, abdominal bloating, indigestion, steatorrhea, weight loss, and anorexia. Even though up to 80% of pancreatic cancer patients eventually present with symptoms related to exocrine pancreatic insufficiency, only 21% are prescribed pancreatic enzyme replacement therapy. This treatment is profoundly underutilized in the palliative care of these patients. The objective of this review is to discuss the pharmacology, pharmacokinetics, side effects, available evidence of effectiveness of pancreatic enzyme use for patients with pancreatic cancer, and challenges along with proposed solutions regarding its use. Pancrelipase is an expensive drug, and it is inactive if not taken correctly. The impact of symptoms of EPI can lead to poorer overall well-being. Pharmacists play a crucial role in properly educating patients on the correct use of pancreatic enzyme replacement therapy. Pancreatic enzyme replacement therapy (PERT) is a key strategy in managing symptoms of EPI and can improve quality of life, which is a central focus in palliative care.

Keywords: pancreatic cancer; exocrine pancreatic insufficiency; pancreatic enzymes; palliative care; medication instruction

1. Introduction

Every year about 64,000 patients are newly diagnosed with pancreatic cancer in the United States alone. It is considered the fourth leading cause of cancer-related deaths for both sexes while its 5-year survival rate is as low as 12% [1]. Most of the tumors arise from the ductal epithelium of the head of the pancreas causing mechanical obstruction of the flow of pancreatic juice resulting in exocrine pancreatic insufficiency (EPI) [2]. A multi-institutional series of 185 exocrine pancreatic cancer patients documented its most common signs and symptoms: asthenia (86%), anorexia (83%), weight loss (85%), abdominal pain (79%), jaundice (55%), pale or clay-colored stools (54%), nausea (51%), diarrhea (44%), vomiting (33%), and steatorrhea (25%), all of which can be exacerbated by EPI [3]. Patients with EPI often describe foul-smelling flatulence, bloating, and exacerbation of pain by eating. Fat malabsorption is common thus patients are likewise prone to having fat-soluble vitamin deficiencies: for example, night blindness due to vitamin A deficiency, metabolic bone disease (i.e., osteomalacia or osteoporosis) due to vitamin D deficiency, increased oxidative cell stress from lack of vitamin E, and bleeding disorders due to vitamin K deficiency [4].

Almost two-thirds of patients with pancreatic head tumors will develop EPI, which increases to 9 out of 10 over the course of the illness [5]. Contributing factors for developing EPI in pancreatic cancer include obstruction of the main pancreatic duct by the tumor itself, reduced cholecystokinin secretion, bicarbonate delivery, and loss of primary parenchyma, including from surgical resection and irradiation [6]. Significant nerve damage after lymph node dissection during pancreatic surgery

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can also lead to asynchrony between bile and enzyme delivery, and reduced stimulation of the pancreas.

Diagnostic imaging studies such as computed tomography scans, magnetic resonance imaging and endoscopic ultrasound cannot precisely diagnose EPI. Individuals with severe EPI exhibit increased fecal fat concentration. Fecal elastase test is the most sensitive and specific test of pancreatic function; however, testing is not a pre-requisite in starting pancreatic enzyme replacement therapy (PERT) because of the high prevalence of EPI among pancreatic cancer patients [7]. Empirical treatment with pancrelipase is recommended in patients suspected of having fat malabsorption. Fecal elastase is an enzyme product of pancreatic secretion which remains stable throughout the gastrointestinal tract. Values of 100-200 micrograms/gram of stool signify mild to moderate pancreatic insufficiency, while less than 100 micrograms/gram of stool indicate severe EPI. However, watery diarrhea may lead to false positive test result due to dilution of fecal specimen. Crohn's disease, bacterial overgrowth, lactose intolerance, giardiasis, cholestasis and other biliary diseases, colitis, celiac disease, and short bowel syndrome, which are all diseases that impact mucosal fatty acid uptake, can also cause abnormal values [22]. These conditions should be considered if a patient has poor response to PERT, as concomitant gastrointestinal comorbidity can also occur.

A patient-reported outcome instrument was developed to assess EPI symptoms, and its unfavorable impact on health-related quality of life [8]. A retrospective and non-randomized study of 66 patients with unresectable pancreatic cancer receiving PERT with standard palliative care (PC) versus standard PC alone, showed that the median survival was longer (301 days vs 89 days) for the former group [9]. Poorly controlled malabsorption symptoms of patients with pancreatic cancer can significantly impact their quality of life. The unpredictable occurrence of gastrointestinal symptoms can limit their travel, disrupt their desired activities, and social engagements, leading to isolation and emotional distress [10].

Palliative medicine is an integral part and the mainstay of treatment of pancreatic cancer patients. EPI symptoms can be alleviated by PERT; however, this is not typically taught in palliative care. The objective of this article is to provide a review of pancrelipase and how palliative care clinicians can use it to palliate symptoms related to pancreatic cancer.

2. Normal Physiology

The pancreas secretes 1.5 liters of pancreatic juice that is rich with enzymes to digest fats, proteins, and carbohydrates. Both hormonal and neuronal mechanisms regulate the secretion of pancreatic juice. Two hormones that provide negative feedback mechanism are secretin and cholecystokinin. Secretin is released from enteroendocrine cells in the small intestine. It stimulates the pancreas to release a bicarbonate-rich fluid, which is important to neutralize gastric acid as it enters the duodenum. Cholecystokinin stimulates the pancreatic acinar cells to release digestive enzymes through the vagal afferents. It is released in response to the presence of proteins and fats in the small intestine from ingested food [11].

3. Pharmacology

Common indications for PERT include pancreatic cancer, intraductal papillary mucinous neoplasms, premalignant mucinous cystic lesions, benign tumor of the pancreas, pancreatectomy, cystic fibrosis, and chronic pancreatitis [12,24]. Pancreatic ductal adenocarcinoma represents the predominant subtype of exocrine pancreatic cancer by over 90 percent and has an overall 5-year survival rate of only 8.5 percent [13,14]. Cystic fibrosis is the most common cause of EPI among children which is detrimental as it can affect their growth patterns attributed to nutrient malabsorption [15]. Conversely, chronic pancreatitis is the primary cause of EPI among adults [12]. Incremental inflammation of the pancreas related to chronic pancreatitis can lead to the deterioration of pancreatic parenchyma and subsequently pancreatic insufficiency resulting in malnutrition, weight loss and steatorrhea [16].

PERT helps improve digestion and absorb nutrients. The capsules are not systemically active substances as the enzymes are not directly absorbed from the gastrointestinal tract [17]. The capsules

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are enteric coated to help resist its destruction when it reaches the acidic environment of the stomach. The enzymes are only released when the capsule reaches the duodenum with a higher level of pH 5.5 [18]. Patients who benefit from PERT have a dramatically decreased fecal fat content [19]. The fundamental principle is that enough pancreatic enzyme should be mixed with food at an appropriate pH environment for the greatest enzymatic activity. The patients should strictly adhere to detailed instructions specific to PERT administration as discussed further below.

PERT can also be administered through enteral tubes. It can be mixed with nectar thick fruit juice for easier delivery and to prevent clumping in the tube [20]. It can also be mixed with sodium bicarbonate to dissolve the enteric coating and allow for improved activation in a higher pH environment [21].

4. Pharmacodynamics

The inability to digest fat completely leads to the major maldigestion or malabsorption problems. In clinical trials, the administration of pancrelipase as a mixture of amylase, lipase, and protease showed a significant improvement in the coefficient of fat absorption and nitrogen absorption and were accompanied by increases in body weight and body mass index [15].

Up to 85 percent of pancreatic cancer patients are expected to have weight loss [3]. A small trial of combined intervention of pancreatic enzyme therapy for 8 weeks with dietary counseling resulted to 0.7-kilogram improvement in body weight compared to 2.2-kilogram weight loss for those in placebo group among patients with unresectable pancreatic head mass [22]. This may indicate that administration of PERT can prevent further weight loss given active treatment against fat malabsorption. Another study showed improvement in feeling of indigestion, light-colored yellow stools, and visible food particles in stool for those patients who took PERT appropriately [23]. One observational study involving PERT use among patients with unresectable pancreatic cancer found improvement in body mass index by 1.01 (versus 0.95 in placebo group, p=<0.001), even while receiving chemotherapy [21]. Symptoms of fat malabsorption do not become clinically evident until secretion of lipase is less than 10 percent of normal levels, highlighting the substantial reserve capacity of the pancreas [25].

5. Mechanism of Action

The capsules contain a combination of lipases, proteases, and amylases that catalyze the hydrolysis of fats to glycerol and fatty acids, proteins into peptides and amino acids, and starch into dextrins and short-chain sugar, respectively [18].

6. Absorption

PERT is minimally absorbed from the gastrointestinal tract; hence it is not absorbed into the bloodstream in any significant amount, and therefore is not systemically active. Its effects are confined in the intestinal lumen, where it helps break down the food into absorbable components [12].

7. Volume of Distribution

Pancrelipase acts locally in the gastrointestinal tract, and it is not absorbed in any significant amount, thus the volume of distribution is not relevant [12].

8. Protein-Binding

Pancrelipase acts locally in the gastrointestinal tract, and it is not absorbed in any significant amount, thus the protein-binding is likewise not relevant [12].

9. Metabolism

Pancrelipase acts locally in the gastrointestinal tract, and it is not absorbed in any significant amount, thus the metabolism is not relevant [12].

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10. Route of Elimination

Pancrelipase is eliminated in the feces entirely [12].

11. Half-Life

Pancrelipase acts locally in the gastrointestinal tract, and it is not absorbed in any significant amount, thus the elimination half-life is not relevant [12].

12. Clearance

Pancrelipase acts locally in the gastrointestinal tract, and it is not absorbed in any significant amount, thus the clearance rate is not relevant [12].

13. Dosing and Formulation

CREON® (pancrelipase) is a commonly available pancreatic enzyme replacement therapy. It was the first PERT to be approved by the Food and Drug Administration (FDA) in 2009. The capsule comes as follows, see Table 1:

Table 1. Dosage Forms and Strengths of CREON® from Food and Drug Administration.

Dosage Forms	Lipase	Protease	Amylase
"CREON®"			
"CREON 1203"®	3,000 USP	9,500 USP	15,000 USP
"CREON 1206"®	6,000 USP	19,000 USP	30,000 USP
"CREON 1212"®	12,000 USP	38,000 USP	60,000 USP
"CREON 1224"®	24,000 USP	76,000 USP	120,000 USP
"CREON 1236"®	36,000 USP	114,000 USP	180,000 USP
"ZENPEP®"			
"EURAND 5" or Zenpep 5®	5,000 USP	17,000 USP	27,000 USP
"EURAND 10" or Zenpep 10®	10,000 USP	34,000 USP	55,000 USP
"EURAND 15" or Zenpep 15®	15,000 USP	51,000 USP	82,000 USP
"EURAND 20" or Zenpep 20®	20,000 USP	68,000 USP	109,000 USP
"PANCREAZE®"			
"McNEIL, MT 4" or Pancrease 4200®	4,200 USP	10,000 USP	17,500 USP
"McNEIL, MT 10" or Pancrease 10,500®	10,500 USP	25,000 USP	43,750 USP

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"McNEIL, MT 16" or Pancrease 16,800®	16,800 USP	40,000 USP	70,000 USP
"McNEIL, MT 20" or Pancrease 21,000®	21,000 USP	37,000 USP	61,000 USP
	"PERTZYE®"		
"DCI 4" or Pertzye 4®	4,000 USP	14,375 USP	15,125 USP
"DCI 8" or Pertzye 8®	8,000 USP	28,750 USP	30,250 USP
"DCI 16" or Pertzye 16®	16,000 USP	57,500 USP	60,500 USP
	"VIOKACE®"		
"VIO9111" or Viokace 10,440®	10,440 USP	39,150 USP	39,150 USP
"VIO9116" or Viokace 20,880®	20,880 USP	78,300 USP	78,300 USP

USP: United States Pharmacopeia.

Pancrelipase dosing is based on lipase units. The starting dose is 500 lipase units per kilogram of body weight per meal. Dosage should vary based on the fat content in the diet, clinical symptoms, and severity of steatorrhea [12]. A reduction in steatorrhea of up to 15 grams fat per day is observed when PERT of 25,000 to 40,000 IU of lipase per meal is supplemented. However, doses should largely be dependent on the severity of disease and size of the meal [26]. Additionally, one half of the computed dose per patient is recommended to be administered with snacks.

PERT are not bioequivalent and are not interchangeable. The dosage formulations differ in their concentrations of lipase, protease, and amylase. The FDA has approved five enteric-coated formulations: CREON®, ZENPEP®, PANCREAZE®, PERTZYE® and RELIZORB®, which are designed primarily for patients who still maintain normal gastric acid secretion. A microencapsulated formulation is crucial to prevent the enzyme from deactivation. Both PERTZYE® and RELIZORB® are designed for use in gastrostomy tubes. VIOKACE® is a non-enteric coated formulation that is thought to mix well with intragastric contents and can rapidly release lipase in the duodenum for fat digestion, however it is only prescribed for adult patients also treated with a proton pump inhibitor (PPI). The acid suppression action of a PPI prevents denaturation of uncoated exogenous pancreatic enzyme (i.e., VIOKACE®).

Table 2 below indicates the recommended guidelines for PERT dosages across various age categories [25,27–29]:

Age group	Units of lipase
Infant	2,000 – 4,000 units per 120 mL formula or breastmilk. Dosing can be challenging due to varying degree of fat content in breastmilk or formula.
Child aged less than 4 years	1000 units per kilogram per meal 500 units per kilogram per snack
Child aged 4 and above	500 units per kilogram per meal 250 units per kilogram per snack
Adult starting dose	50,000 units per meal 25,000 units per snack
Adult maximum dose	150,000 units per meal 70,000 units per snack

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14. Toxicity and Adverse Effects

The studies of the toxicology of pancrelipase are not needed as this drug has been used clinically for a long time [12]. Clinical overdose studies proved no effect on lungs, pancreas, liver, and kidneys but it can produce symptoms such as diarrhea and stomach upset. Carcinogenicity studies have not shown any increased incidence with the use of pancrelipase.

There is no contraindication in starting PERT and there is no known drug-drug interaction. As pancrelipase is not absorbed, effect on fetal development or reproduction is not expected. It is not known whether this is excreted in milk, but it can be safely given to pregnant women (pregnancy category C). This is generally a well-tolerated product although rare side effects include oral irritation, which is typically observed for those who retain the capsule in their mouth or chew the capsule, which is not advisable. An increase in serum uric acid is noted therefore caution is advised among those with concomitant gout or hyperuricemia. Since the enzyme is derived from porcine sources, patients with a pork allergy should be advised accordingly. Fibrosing colonopathy has been reported as a side effect of PERT, which is typically found in patients with cystic fibrosis who require higher doses of pancreatic enzymes [12]. Patients who have Muslim or Jewish backgrounds who may avoid pork products due to religious reasons should be counseled regarding the origin of PERT. However, some religious authorities have granted its use as there is no formal alternative available [30]. It is essential for healthcare providers to collaborate closely with the patients and to consider cultural and religious sensitivities when prescribing treatments.

15. Drug Interactions

Pancrelipase can cause a decrease in the absorption of ferric sulfate resulting in a reduced serum concentration and potentially a decrease in efficacy [12].

16. Food Interactions

Patients should be instructed the following: drink plenty of fluids, take with fluids and food, and if swallowing the oral capsule is not tolerated, it can be sprinkled on acidic soft foods with a pH of 4 or less [12].

17. Assessment of Response to Therapy

The effectiveness of PERT can be assessed through clinical indicators such as decreased fat in the stools, gain in body weight and improvement in stool consistency.

18. Challenges and Proposed Solutions

The main problem with PERT is its underuse among patients with pancreatic cancer. In a retrospective study of 4,554 patients with pancreatic cancer, only 21.7% were prescribed PERT when in fact the prevalence of EPI is high [31].

Incorrect timing of PERT administration is another barrier to use. Patients should be counselled to take PERT at the time of food consumption, as the medication degrades within 10 minutes of intake. One article showed misconceptions how to take PERT: one patient inadvertently placed it in the pillbox and did not take it with meals while another reported forgetting to bring it when he goes out to eat at restaurants [32]. A prospective, randomized, crossover study concluded that the group who took PERT at the time of meals and during meals showed better fat digestion compared to those who took it before meals and just after meals [33].

A study by Landers et al. showed that patients taking PERT understood its complex medication titration as well as its appropriate use, which was opposite from the study done by Garcia et al [32,34]. However, all the participants enrolled in the latter study were older adults (i.e., age 65 and above) wherein cognitive impairment and health literacy may be contributing factors for poor knowledge regarding its proper intake.

Additional PERT capsule is required for larger meals or higher fat content meals. Inadequate improvement in EPI symptoms despite PERT intake might suggest the necessity of escalating its

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dosage. The patients might not be aware that nutritional or shake-style supplements, and vitamin D (a fat-soluble vitamin) require concomitant PERT use. A handout can be provided detailing the following: (1) "Gather pancreatic enzyme capsules before meals and snacks, (2) Take pancreatic enzyme capsules with cold or room temperature liquids with the first bite of food or nutritional drink (e.g., Ensure or Glucerna). Take the capsule whole. Do not crush or chew it, (3) Set timer for 10 minutes. If you are still eating after 10 minutes, take another capsule and repeat until you are finished with your meal or drink, (4) Notify your physician if you continue to experience abdominal bloating, cramping, burping, increased frequency of stools or if stools continue to appear oily (steatorrhea) [32]."

An additional cause for under-prescribing PERT may be related to the financial burden for a supportive care intervention. An analysis of 2020 Medicare Part D plans noted that expected out-of-pocket costs for optimally dosed PERT across the five formulations ranged from United States Dollar (USD) 853 to USD 1,536 per month for those paying a deductible and coinsurance, to USD 527 to USD 1,210 for refills made after meeting the deductible for a 30-day supply [35].

Patients with pancreatic cancer also warrant a nutritionist referral due to significant anorexia and weight loss, as nutritional supplements may be helpful [36]. Each patient's needs are unique, and a nutritionist can provide tailored dietary advice and modifications to manage symptoms of EPI. A nutritionist can also suggest strategies to ensure adequate intake of PERT. Referring a patient with pancreatic cancer for dietary counseling is a key component of multidisciplinary approach to patient care.

Patients with pancreatic insufficiency were traditionally managed by limiting the amount of daily fat intake, however this led to further restriction of fat-soluble vitamin intake. The fundamental change in approach was then to limit foods that are difficult to digest (i.e., legumes) and advising the patients more frequent but low-volume meals [16,38].

If there is an insufficient response to initial therapy, two options to trial are: (1) to add a proton pump inhibitor (PPI) to decrease gastric acidity (PERT is denatured in gastric acid of the stomach), or (2) to increase the dose of enzyme units as the dose that is needed is probably higher [37]. The maximum dose is 2,500 lipase units per kilogram of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day) [11]. Interestingly, a case report was published involving unmasking symptoms of pancreatic insufficiency when a pancreatic cancer patient inadvertently discontinued his PPI. The patient was not initially presenting EPI-related symptoms hence he was not prescribed PERT, likely because of his chronic use of PPI which led to a decrease in bicarbonate production and secretion. Within a few weeks of restarting both PPI and PERT, the patient's malabsorption symptoms have resolved [39].

19. A Case Report Highlighting Challenges with Regards to PERT Prescription Is as Follows

A 65-year-old man was diagnosed with metastatic pancreatic cancer refractory to multiple lines of therapy. His most burdensome symptoms were abdominal bloating, steatorrhea, and diarrhea, which restricted his capacity to leave the house. He was then referred to palliative medicine due to his complex medical needs. His condition raised concerns for moderate protein-calorie malnutrition. Upon establishing care with a palliative care clinician, the patient was already taking hydromorphone as needed for pain and CREON® 1206, containing 6,000 USP of lipase, 19,000 USP of protease and 30,000 USP of amylase, to aid digestion. However, despite his prescriptions, his adherence to CREON® was irregular, particularly in timing with meals. The patient admitted forgetting to take his CREON® capsule with meals as he inadvertently placed it in his pillbox, together with his routine medication regimen. He likewise revealed that when he dines out at a restaurant, he forgets to bring the capsule with him and rather takes it as soon as he gets home. The CREON® dose was further increased and education regarding its correct administration was provided. Recognizing the need for specialized nutritional intervention, the palliative care team referred him to a nutritionist. The nutritionist conducted a thorough assessment of the patient's dietary habits, emphasizing the importance of taking CREON® with meals. The patient also began taking CREON® with his nutritional supplement or meal replacement shake (i.e., Ensure), a practice he was previously unaware of. Gradually, with consistent use of CREON® with meals and adherence to the tailored dietary plan, the patient reported a significant improvement in his symptoms, and was able to taper

off his hydromorphone usage. This eventually led to a positive effect in his overall well-being. The collaboration between palliative care, nutrition, and the patient himself proved crucial in managing his exocrine pancreatic insufficiency, highlighting the importance of an interdisciplinary strategy in complicated cases.

Regrettably, as his pancreatic cancer advanced, he became unable to tolerate any oral intake. He was subsequently placed in hospice or comfort care at home. Afterwards, the CREON® was discontinued since he could no longer tolerate oral intake.

20. Conclusion

Patients with pancreatic cancer typically present with pain, vomiting, diarrhea, and steatorrhea, which heavily impact their quality of life affecting their day-to-day functioning and restricting social relationships. PERT can improve gastrointestinal symptoms and survival; however, it is underutilized in palliative care. Suboptimal patient instruction with regards to PERT use may also lead to poor patient adherence. Pharmacists play an important role in educating patients with pancreatic cancer in the proper use of PERT. A combination of dietary counseling, comprehensive PERT education and regular medication reviews especially for older adults are important considerations in ensuring a holistic approach in managing symptoms of pancreatic cancer. It is essential to manage pancreatic cancer symptoms using PERT, as this approach can potentially minimize a patient's opioid usage and use of anti-diarrheal medications, although further studies are warranted.

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