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Progress report

Pancreatic extracts in the treatment of pancreatic exocrine insufficiency

One of the principal results of pancreatic disease is that the pancreas secretes less hydrolytic enzyme than normal into the duodenum in response to the stimulus of food. However, the reserve capacity of the exocrine pancreas is such that the defective digestion of fat, protein, and starch is not observed until the secretion of lipase[1,2], trypsin[2], and amylase[3] is less than 10% of normal values.

When pancreatic exocrine secretory capacity is reduced so severely that maldigestion results, a range of clinical disorders may develop[4] and specific treatment becomes necessary. The aim of the specific therapy is to replace the pancreatic enzymes, which can no longer be secreted, by orally administered enzymes, so that the enzymic activities attained in the duodenum and small intestine become sufficient to prevent maldigestion of the principal foodstuffs. Effective therapy therefore necessitates:

Satisfactory Pancreatic Extracts

Obviously, for replacement therapy to be effective, the administered pancreatic enzymes must be satisfactory. The majority of the available preparations of pancreatic enzymes are derived from extracts of the pancreas of slaughtered animals (particularly cows and pigs). Recently, preparations have been marketed which include proteases of vegetable origin[5] and it has also been suggested that lipases of bacterial origin may prove therapeutically useful[6].

The enzymic activities of some preparations of pancreatic extracts have been analysed[7,8,9,10] but the commercial availability of these products varies and new products or new sources of pancreatic extract are developed, so that little is known about the uniformity or degree of variability of the enzymic activity of currently obtainable extracts. These problems will be discussed in more detail elsewhere[11] but it must be emphasized that, at present, only very limited information is available about the activities of the replacement enzymes ingested by most patients.

Ingestion of the Replacement Enzymes by Patients

The general unreliability of intake of prescribed therapeutic agents has already received comment[12]. No specific information is available about the acceptability to patients of pancreatic extracts but some points require emphasis.

Patients with maldigestion due to pancreatic disease are highly motivated to ingest replacement enzymes, if the treatment is successful, since satisfactory replacement therapy gives patients a marked feeling of well-being, while cessation of treatment is accompanied by rapid subjective and objective

deterioration in health[13]. However, pancreatic extracts are variably unpalatable and also quite frequently nauseating, both of which factors militate against reliable intake.

Satisfactory Delivery of Replacement Enzymes to the Site in the Alimentary Tract where Digestion Takes Place and Adequate Mixing of the Enzymes with Food

The site in the alimentary tract where enzymic digestion of food occurs is determined by the presence of the correct milieu and of the appropriate cofactors for the satisfactory function of the enzymes. Factors which are known to influence the activity of all the pancreatic enzymes include the pH[14,15,16,17,18,19,20,21] and calcium content[22,23,24] of the enzymic environment and perhaps also the presence or absence of adsorptive surfaces[25,26,27,28]. Known factors which influence the activities of the individual enzymes or their zymogens include the presence of bile salts[29,30] and colipase[31,32,33,34] for lipase, chloride[35] for amylase, and enterokinase[15,36] and bile salts[37] for trypsinogen. The site of maximal enzymic activity is therefore determined principally by pH and by the presence of bile salts and colipase.

THE pH OF THE ENZYMIC MILIEU

The pancreatic enzymes are rapidly and irreversibly inactivated by acid and the enzymic degradation is even more rapid and complete under the influence of the proteolytic action of pepsin[38]. The presence of gastric juice is therefore one of the principal determinants of the failure of replacement therapy.

The acid-secretory capacity of the stomach of patients with alcohol-induced pancreatic exocrine insufficiency may be markedly impaired in response to exogenous stimulants[39,40,41,42,43,44,45], indicating the coincident occurrence of severe gastric disease. Gastric secretion in non-alcoholic chronic pancreatitis may be normal or greater than normal[43,46] and may be associated with an increased incidence of duodenal ulceration[47,48,49,50,51]. In addition to low intragastric pH, when normal or excessive capacity to secrete acid coincides with defective capacity to secrete bicarbonate in patients with pancreatic exocrine insufficiency, conditions unfavourable to enzymic activity (low pH) may also extend throughout the small intestine[52], although the evidence is controversial[53].

Attempts have been made to counter the possibility that the enzymes of the pancreatic extracts may undergo inactivation by acid and pepsin during transit through the stomach by:

Administration of coated preparations of the pancreatic extracts

The physical form in which pancreatic extracts are administered orally is an important determinant of the enzymic activity at different levels of the small intestine. When pancreatic extract is given in the form of a powder mixed with food, pancreatic enzymes will be present wherever in the intestine there is food, and whenever the circumstances are appropriate for satisfactory enzymic activity. However, the unpleasant taste of pancreatic extracts and, more important, the danger of inactivation of the pancreatic enzymes during gastric transit have led manufacturers to coat the pancreatic extract with acid-resistant capsules. No information is yet available about the adequacy

of disintegration of the coated preparations at sufficiently high levels of the small intestine to ensure optimal conditions for mixing with, digestion of, and subsequent absorption of food materials.

Administration of antacids

The use of antacids in conjunction with pancreatic extract seems appropriate since antacids not only buffer gastric acid but irreversibly inactivate pepsin by raising the intragastric pH[54,55,56]. The administration of sodium bicarbonate alone has been reported to correct at least one of the aspects of the digestive dysfunction of patients with chronic pancreatitis (malabsorption of vitamin B_{12}[57,58,59]), while the administration of sodium bicarbonate with the pancreatic extract has been found to improve the steatorrhoea of chronic pancreatitis[60,61,62]. No quantitative data are available but it seems probable that the more of the secreted acid which is buffered, the better the chance of satisfactory gastric transit for the therapeutic pancreatic extracts. The quantity of acid which is secreted in response to a meal is approximately equal to the maximal response to exogenous secretagogues[63,64]. Although some of the acid secreted in response to a meal is buffered by the protein components, it is usually necessary to provide more antacid than the equivalent of maximal acid secretory capacity, since antacid buffer is emptied from the stomach quite rapidly[65].

No systematic investigation has been undertaken to determine the antacid which is most suitable for use with pancreatic extracts. In this connexion, two points require emphasis. Although disturbances of calcium metabolism, leading to osteomalacia, are rare in association with the steatorrhoea of pancreatic exocrine insufficiency[66,67,68,69], calcium-containing antacids are useful both to augment the intake of calcium and because the calcium-containing antacids are very efficient buffers[70,65,71]. However, when satisfactory pancreatic replacement therapy abolishes steatorrhoea, severe constipation may result[13], so that magnesium-containing antacids may then become particularly useful, in view of their laxative properties.

Administration of gastric secretory inhibitors

The quantity of antacids administered with pancreatic extracts may be reduced by also giving drugs which suppress food-stimulated acid secretion. Anticholinergic drugs have been used for this purpose, but suppress food-stimulated acid secretion by only about 30%. Metiamide, an H_2-receptor antagonist which has been shown to suppress the gastric secretory response to food by about 70%[72], has also been used in patients with chronic pancreatitis with excellent results, so that even the previously untreatable steatorrhoea of patients with chronic pancreatitis and associated duodenal ulcer has become manageable[73].

THE PRESENCE OF BILE SALTS

No quantitative information is yet available about the role of bile salts in the steatorrhoea of pancreatic exocrine insufficiency. In patients with pancreatic or ampullary cancer, obstruction of the bile duct is often complete, so that pancreatic replacement therapy alone cannot cure the steatorrhoea. In patients with chronic pancreatitis who have undergone surgical translocation of the biliary outflow, eg, cholecyst-jejunostomy, similar, although usually

less severe, problems may arise since mixing of bile salts, food, and pancreatic enzymes is variably suboptimal.

In patients with chronic pancreatitis there are often abnormalities of the motor interaction of biliary system, duodenum, and stomach which result, for example, in severe duodenogastric reflux[74,75]. The functional implications of these abnormalities are not known and it is not clear to what extent regurgitation of bile into the stomach affects the small intestinal intraluminal concentration of bile salts.

Although mixtures of pancreatic extract with bile salts are available commercially, their palatability is less than pancreatic extracts alone and they are therefore unacceptable and therapeutically unsatisfactory. No satisfactory direct solution to the problem of treating combined pancreatic exocrine and biliary deficiency has yet been developed.

THE PRESENCE OF COFACTORS

No information is available about the presence of colipase in pancreatic extracts.

The enterokinase activity of the duodenal contents is functionally adequate in pancreatic exocrine insufficiency[76]. In any case, enterokinase is not necessary for the activation of the enzymes of pancreatic extracts since the proteases of these extracts are present in fully activated form.

Assessment of the Efficacy of Treatment

Since the purpose of replacement therapy with pancreatic extracts is to cure the maldigestion associated with pancreatic exocrine insufficiency, the success or failure of the treatment can be inferred from the degree of reversion to normal of the maldigestion of food. Clinically, a measure of the efficacy of replacement therapy is therefore provided by monitoring the faecal excretion of fat and nitrogen during treatment. It is necessary to adjust the dosage and form the pancreatic extract, and of the ancillary therapeutic agents, until steatorrhoea and creatorrhoea revert to normal.

If replacement therapy fails to cure the maldigestion, then either insufficient pancreatic extract is present in the small intestinal lumen or some other factor is involved. A rapid guide to the adequacy of the intraluminal content of the pancreatic enzymes during treatment with powdered pancreatic extract is provided by measurement of the content of pancreatic proteases in 24-hour samples of faeces, collected after purgation[77]. Normal amounts, particularly of chymotrypsin, indicate that the persistence of steatorrhoea and creatorrhoea is due to coincident disease.

Conclusion

Pancreatic replacement therapy can, and should, cure the maldigestion of pancreatic exocrine insufficiency. It is necessary to ensure that the patients ingest satisfactory pancreatic extracts in a suitable form and that the enzymes pass through the stomach intact. In patients with normal gastric secretory function, it is therefore usually necessary to give antacids and to inhibit gastric secretion to ensure that the pancreatic extract passes through the stomach without being inactivated.

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