Medical Treatment of Chronic Pancreatitis

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Abstract

The medical treatment has an important role in patients with chronic pancreatitis. Pain is the most frequent symptom, at least in the initial phases of the disease. In about 60% of patients it can be successfully treated by medical therapy; in the remaining 40% it requires surgery. Malabsorption of fat and protein and diabetes usually appear in the advanced stages of the disease. The treatment of these complications is based on the administration of pancreatic extracts and insulin. There are several types of pancreatic extracts; the most useful are those with high lipase content and high lipase-protease ratio. Moreover, they should be protected against gastric acid and should have a gastric emptying simultaneously with chyme, with a rapid liberation of enzymes into the duodenum. The treatment of diabetes usually requires low-moderate doses of insulin. Diabetic chetoacidosis is rare, while microvascular changes have the same frequency as in type 1 diabetes.

Key words: Chronic pancreatitis, diabetes, medical treatment, pain, steatorrhea, pancreatic extracts.

Introduction

Pain, steatorrhea, and diabetes are the main clinical manifestations of chronic pancreatitis. While the treatment of steatorrhea and diabetes is only medical, the treatment of pain may require surgery. In this article, I will discuss the medical measures usually employed in the treatment of these symptoms. Medical treatment may be useful even in some complications of chronic pancreatitis such as pancreatic pseudocysts, pancreatic ascites, and pancreatic fistulas in which treatment with octreotide may correct the complication.

Treatment of pain

Pain is the most frequent symptom in patients with chronic pancreatitis (95% of cases), especially during the early phases of the disease (1, 2). Usually, it is intense and recurrent, and it is the main reason for hospitalization of these patients. Medical treatment may be simple, but in several cases it is difficult or without effect, and surgery is necessary. A high percentage of the patients, generally 30-40%, are operated on for pain (1, 2). While the clinical characteristics of this symptom are well known, the mechanisms responsible for its appearance and persistence are not completely understood. The most important pathogenetic mechanisms are believed to be increased ductal and interstitial pressure (3-5), damage to pancreatic nerves (6-8), active inflammation (1, 2), and enlarging pseudocysts (9, 10). This multiplicity of pathogenetic mechanisms explains, at least in part, the difficulty often involved in its treament.

Pain in chronic pancreatitis poses problems of prevention and treatment (Tab. I). The prevention is difficult and there are no measures capable of reaching this objective with certainty. However, the most important measure that

Riassunto

TRATTAMENTO MEDICO DELLA PANCREATITE CRONICA

Il trattamento medico ha un ruolo molto importante nella pancreatite cronica. Il dolore è il sintomo più frequente della malattia, soprattutto nelle fasi iniziali del suo decorso. In circa il 60% dei pazienti può essere trattato con la terapia medica; nel rimanente 40% è necessario l'intervento chirurgico. Il malassorbimento e il diabete generalmente compaiono nelle fasi avanzate della malattia; il loro trattamento si basa sulla somministrazione di estratti pancreatici e di insulina. Vi sono numerosi tipi di estratti pancreatici; i più utilizzati sono quelli ad alto contenuto di lipasi e con elevato rapporto lipasi-proteasi. Inoltre, devono essere protetti dall'acido gastrico e devono avere uno svuotamento gastrico simultaneo col chimo, con rapida liberazione degli enzimi nel duodeno. Il trattamento del diabete richiede la somministrazione di insulina; in genere sono sufficienti dosi basse o moderate. La chetoacidosi diabetica è rara, mentre le alterazioni microvascolari hanno la stessa frequenza che nel diabete tipo 1.

Parole chiave: Pancreatite cronica, diabete, trattamento medico, dolore, steattorea, estratti pancreatici.

Tab. I – TREATMENT OF PAIN IN CHRONIC PANCREATITIS

– Discontinue alcohol and smoking	
– Analgesics (ketoprofen, diclofenac, meperidine, pentazocine)	
– Celiac plexus block	
– Sandostatin (if pain is due to pseudocysts not communicating with the Wirsung duct)	
– Pancreatic enzymes (?)	
– Antioxidant therapy (?)	
– Stents	in selected
– Removal of pancreatic stones	cases
– Surgery	

can be taken in alcoholic pancreatitis is the suppression of alcohol use. Generally, this tends to reduce the frequency of painful attacks and contribute to a better prognosis of the disease (1, 2, 11). Since most of these patients are heavy smokers, it is useful to suggest the abolition of smoking too. In the nonalcoholic forms of chronic pancreatitis, the cause of the disease should be identified and treated. The use of pancreatic extracts for prevention of pain is controversial. So far, five studies have been published (12-16); in two of these (12, 13) some benefit was reported, whereas in the remaining three (14-16) no beneficial effect was found. The reason for this difference is not clear; however, it should be noted that in the first two studies an enzyme preparation in tablet form was used, whereas in the other three studies microspheres were used. Whether the type of enzyme preparation may have a role in determining its analgesic efficacy is difficult to say.

The treatment of the attacks of pain requires analgesics. Usually, we use the nonsteroideal anti-inflammatory drugs (ketoprofen, diclofenac) two-three times daily with good success in several cases. If these drugs are not effective, we use stronger analgesics such as meperidine or pentazocine, which usually block pain. If pain is due to an enlarging pseudocyst which does not communicate with the Wirsung duct, we use octreotide, 0.1 mg three times daily, which is helpful in about 60% of these cases, both in relieving pain and in treating the pseudocyst (9, 10).

For patients whose pain persists, a celiac plexus block is a good measure. Unfortunately, there have been only a few studies on this technique, but they show that it is usually effective in relieving pain, at least for some months (17-19).

There are no other effective neurolytic treatments for pain in these patients. Ballegaard et al. (20) studied the effect of acupuncture and transcutaneous electric nerve stimulation for the treatment of pain in 23 patients with chronic pancreatitis and found that neither technique brought about relief of pain that could substitute for or supplement medical treatment. Medications that might modify neural transmission, including amitriptyline and doxepin, have been ineffective (21). Other techniques for modifying neural transmission such as bilateral splanchnic nerve denervation, interpleural analgesia, and celiac plexus block using endoscopic ultrasonography are currently being evaluated (21).

Patients with chronic pancreatitis may have deficiency in antioxidants (22). It has been reported that antioxidant therapy is beneficial in relieving the course of pain in these patients (23). However, additional studies are required to substantiate these data.

In recent years, several investigators (24-27) have reported that the endoscopic placement of stents within the pancreatic duct or removal of pancreatic ductal stones by endoscopy are helpful in improving pain in chronic pancreatitis. However, there have been no randomized prospective trials comparing these procedures to placebo or to surgical treatment. I believe that these techniques should be limited to a few patients.

For patients in whom pain is severe and persisting, surgical treatment should be performed. In any case, surgical treatment should be considered as a last resort, only after all medical measures have failed to relieve pain. It provides significant pain relief in 70-80% of selected patients.

In some cases (10-15%), usually in the early phases of the disease, an attack of acute pancreatitis may develop, which requires a specific treatment. In most of these cases, however, acute pancreatitis is of edematous type, and does not pose particular problems.

Treatment of exocrine pancreatic insufficiency

Exocrine pancreatic function is impaired in almost all patients with chronic pancreatitis (95-100%); the impairment may be mild, moderate or severe (28). Maldigestion of fat and protein with consequent steatorrhea and creatorrhea occurs only in patients with severe insufficiency (less than 10% of normal). In the more advanced phases of the disease, the frequency of this complication is about 60-70%. Mild and moderate insufficiency are usually asymptomatic and do not require particular treatments. The treatment of maldigestion is based on the administration of pancreatic extracts (Tab. II). Many different preparations of pancreatic extracts are available for use in clinical practice, namely powders, granules, tablets, and capsules, enteric-coated and nonenteric-coated. A major problem which exists mainly with the conventional, nonenteric-coated preparations, is that the enzymes are inactivated by acid and pepsin during the gastric passage and only a small part of the ingested enzymes, approximately 10-20%, actually reach the intestinal lumen (29). In this regard, it is to be noted that in patients with chronic pancreatitis gastric acid secretion is normal or even increased in those with more severe insufficiency (30), which further contributes to enzyme inactivation.

Various attempts have been made to overcome the gastric

Tab. II – TREATMENT OF STEATORRHEA IN CHRONIC PANCREATITIS

– Pancreatic extract (microspheres or tablets) 30,000 units of lipase per meal
– Hypercaloric diet
– Reduction of fat intake
– Increase dosage of pancreatic extract or use a different preparation if unsuccessful
– Utilize H2 blocking agents or protein pump inhibitors, if unsuccessful because of gastric acid hypersecretion
– Consider another diagnosis if steatorrhea persists

Tab. III – PREREQUISITES OF A GOOD PANCREATIC EXTRACT

– High lipase content
– High lipase-protease ratio
– Protection against gastric acid
– Gastric emptying simultaneously with chyme
– Liberation of enzymes in the duodenum

acid problem and thus to improve the efficacy of pancreatic extracts. One of the first was the simultaneous administration of sodium bicarbonate together with the pancreatic extracts, and more recently, H2 blockers and proton pump inhibitors have been utilized. However, the addition of these drugs, even if it increases the efficacy of the pancreatic extracts in the control of malabsorption, results in a more complex and expensive therapy, so antacids are not usually used. Presently, the most widely used method to protect the pancreatic enzymes from gastric acid is an enteric coating. The most significant development in this area was the introduction, in the early eighties, of preparations consisting of capsules which contained microspheres of enzymes measuring 1 to 3 millimeter. In turn, each microsphere was covered with an acid-resistant coating. The coating dissolves, and the enzymes are released, at a pH ranging between 5.5 and 6.0. The size of the microspheres plays an important role in determining their gastric emptying with food and their efficacy. Indeed, it has been shown that spheres of 1 millimeter empty significantly faster than those of 2 or more millimeters when ingested together with a meal (31). It is therefore important to utilize preparations with spheres having this dimension.

The other factor which is important for enzyme efficacy is that the coating dissolves rapidly so that the enzymes are released once the spheres arrive in the duodenum. The more proximal the release occurs, the greater the length of intestine over which the enzymes are available to digest a meal.

Because several enzyme preparations are now available, it could be important to know whether there are differences among them. In this regard, a comparative study of four currently available enteric coated microsphere preparations of pancreatin (Pancrex Duo, Nutrizym GR, Pancrease, and Creon) has recently been reported (32). The results demonstrated wide variations among these products. Pancrex Duo contained the largest quantity of enzymes and was highly resistant to acid attack. However, its dissolution characteristics were poor. Nutrizym GR contained quantities of enzymes only very close to its declaration and exhibited a shortfall in amylase. Its acid resistance was moderate at 85% and its dissolution characteristics were poor. Pancrease contained the smallest quantity of enzymes and its acid resistance was poor at 65% but its dissolution characteristics were good. Creon had a high enzyme content, was highly resistant to acid and had good dissolution characteristics. Based on the results of this in vitro study, Creon seems to be the most appropriate pancreatic extract.

In summary, the prerequisites of a good pancreatic extract should be the following: high lipase content; high lipase-protease ratio (lipase can be destroyed by an excess of proteases); protection against gastric acid; gastric emptying simultaneously with chyme and rapid liberation of enzymes in the duodenum (Tab. III).

Concerning the dosage of the pancreatic extract, it is believed that at least 30,000 units of lipase with each meal should be provided. The use of pancreatic extracts is well tolerated and usually free of adverse effects (33). Previous studies have reported two important side effects in patients treated with pancreatic extracts, an abnormal increase in serum and urine uric acid concentration (34), and colonic fibrosis with thickening of the wall and strictures (35). These complications have been described in children affected by cystic fibrosis taking very high amounts of pancreatic extracts. In a recent study of the tolerability and safety of the long-term administration of pancreatic extracts in adult patients with chronic pancreatitis, we did not observe either of the above complications (33).

Recent studies (36) have shown that lipase of bacterial origin is more resistant to gastric acid and to degradation by proteases than porcine lipase and the use in the dog with experimentally induced pancreatic insufficiency has given promising results. In the future, it could represent a good alternative to the traditional lipases so far used. Even more exciting is the possibility, in the future, of gene therapy for exocrine pancreatic insufficiency (37).

Treatment of diabetes

Diabetes usually is a late complication of chronic pancreatitis, appearing after 10 or more years of clinical onset of the disease (1, 2). Usually, at least 80% to 90 % of the pancreas must be destroyed before the development of this complication, whose frequency is of about 50-60%. It is usually due to reduced secretion of insulin. In some cases, resistance to insulin has been found (38). Glucagon from alpha cells may be also reduced (21). Diabetic

chetoacidosis is rare, probably in relation to the preservation of at least some insulin secretion.
It has been thought for many years that vascular changes occur less frequently in this form of diabetes compared to type 1 diabetes. Indeed, we have shown (39) that the risk of developing retinopathy in patients with diabetes due to chronic pancreatitis is similar to that in patients with type 1 diabetes. Similar observations have been made in regard to nephropathy (21). Therefore, the microvascular complications of diabetes in chronic pancreatitis have striking similarities with those in type 1 diabetes.
The treatment of this form of diabetes requires insulin; usually, the dosage is lower than that for most patients with type 1 diabetes because of deficiency in glucagon secretion and the absence of insulin antibodies. The oral agents are sometimes used, but they may have some value only in the initial phases of the complication (Tab. IV).

Tab. IV – TREATMENT OF DIABETES IN CHRONIC PANCREATITIS

– Oral antidiabetic agents (initial phases)
– Insulin (usually low-moderate doses)
– Control for diabetic complications

Treatment of pancreatic pseudocysts, ascites, and fistulas

We have shown that in chronic pancreatitis about 60% of pancreatic painful pseudocysts respond to octreotide treatment (9, 10). The pseudocysts which do not communicate with the Wirsung duct and which are responsible for pain are those which can be successfuly treated with this drug. Pain disappears in 3-5 days, and the pseudocyst disappears in about two months. Treatment may be initially performed for one week, and it should be continued only if pain has disappeared and the pseudocyst has decreased in size. The dosage of octreotide is 0.1 mg three times daily.
Octreotide may be useful even in the treatment of some patients with pancreatic ascites or fistulas (40, 41).

Treatment of other complications

In patients having steatorrhea for many years, deficiency of fat-soluble vitamins including vitamins A, D, E, and K may develop. This should be known and adequately treated.
In conclusion, patients with chronic pancreatitis require a careful medical treatment. Moreover, it is important to follow them with care and control the state of their health at least one or two times every year.

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