



View Point

Pharmacological management of pain in chronic pancreatitis

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Abstract

Pain is the major presenting symptom of chronic pancreatitis. Patients with chronic pancreatitis experience substantial impairments in health-related quality of life. Pain may be considered as the most important factor affecting the quality of life. The pathogenesis of pancreatic pain is poorly understood. The cause of pain in chronic pancreatitis is probably multifactorial. This article discusses the various hypotheses that have been suggested to underlie pain. Special attention is paid to the concept of autonomous central sensitisation and hyperalgesia as a cause of pain. Strict abstinence from alcohol is the first step of chronic pancreatic pain management. As a second step, it is important to exclude treatable complications of chronic pancreatitis, such as pseudocysts. Symptomatic treatment with analgesics is often unavoidable in patients with chronic pancreatitis. Acetaminophen, non-steroidal anti-inflammatory drugs and eventually opioids are suitable. Several trials have been performed with pancreatic enzymes, but a meta-analysis demonstrated no significant benefit in terms of pain relief. The treatment of chronic pancreatic pain requires a multidisciplinary approach that tailors the various therapeutic options to meet the need of the individual patient.

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1. Introduction

Pain is the major presenting symptom of chronic pancreatitis and the majority of patients will have pain at a given time during the course of their disease. There is a male predominance, with males about three to four times more likely to be affected by chronic pancreatitis than females. The age of onset of chronic pancreatitis is approximately 40 years, although patients with hereditary pancreatitis tend to be younger [1]. Often, the onset of chronic pancreatitis is heralded by a severe painful attack, indistinguishable from an acute pancreatitis attack. After the first attack, patients become symptom free. However, with the progression of the disease, the attack frequency increases and the symptom-free periods progressively shorten. Ultimately, continuous pain ensues. In a survey of the Asia-Pacific region, chronic pan-

creatitis presented with pain in 60–100% of patients, ranging from 60% in Japan to 80–100% in other Asian countries [2]. Pancreatic pain is steady and agonising, felt in the epigastrium, and sometimes radiates to the back or left shoulder. Typically, the pain is postprandial, but frequently the pain manifests itself without any relation to the meal. Pancreatic pain is difficult to quantify, mostly persistent, and difficult to manage. The inter- and intra-individual variation of pain in chronic pancreatitis is high, with pain duration varying from intermittent to persistent, and pain intensity ranging from mild to disabling. Pain has immediate consequences on the quality of life of patients as it leads to inability to work and frequent hospitalisation.

Amman and Muellhaupt [3] distinguishes two typical pain patterns in alcoholic chronic pancreatitis. The type A pain pattern, typically observed in acute relapsing pancreatitis, is short-lived and pain episodes usually last less than 10 days and are separated by long pain-free intervals of several months to a year. Nearly all patients with an A-type pain pat-

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tern need to be hospitalised because of severe clinical acute pancreatitis. This pain pattern is estimated to be present in nearly 50% of unoperated patients. B-type pain pattern, seen in more than 50% of patients, is characterised by prolonged periods of persistent pain or clusters of recurrent severe pain exacerbations, lasting two or more days per week for at least 2 months, and requiring frequent hospitalisations. B-type pain is typically associated with local complications, such as pseudocysts, cholestasis and presumptive ductal hypertension. These patients underwent surgery for pain relief [3,4].

2. Aetiology

Excessive alcohol consumption is reported to be the most frequent cause of chronic pancreatitis in industrialised countries [5]. It is estimated that in 60–70% of patients with chronic pancreatitis alcohol use preceded onset of the disease. However, it is thought that genetic or environmental factors must be present before alcoholic pancreatitis develops. To categorise the risk factors, the TIGAR-O risk factor classification system has been developed [5,6]. The risk factors are categorised according to causes that have a toxic-metabolic, idiopathic, genetic, autoimmune, recurrent severe acute pancreatitis-associated and obstructive background. Toxic-metabolic factors include alcohol, hypercalcaemia and hyperlipidaemia [7]. Genetic factors play an important role in the susceptibility to pancreatic injury, severity and evolution of inflammatory process, leading in some cases to chronic inflammation and/or fibrosis. Mutations in the cationic trypsinogen gene (PRSS1) have been identified in patients with hereditary pancreatitis. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) were also found to be associated with pancreatitis as well as the serine protease inhibitor (SPINK1) mutations [8–10]. Another risk factor for the development of chronic pancreatitis is smoking [11]. Smoking also is associated with earlier diagnosis of chronic alcoholic pancreatitis and with the appearance of calcifications and diabetes, independent of alcohol consumption [12]. The category of idiopathic chronic pancreatitis includes patients in whom a clear associated factor is not present [5].

The anatomical changes in chronic pancreatitis include irregular sclerosis of the pancreatic gland with destruction and loss of exocrine parenchyma, dilation of the ductal system associated with strictures or stones, or inflammatory cell infiltration. The islets appear to be spared somewhat when compared with acini. The pathogenesis of pancreatic fibrosis has received increasing attention over the past few years, largely due to the identification and characterisation of stellate cells in the pancreas. Repeated episodes of acute pancreatitis and thus exposure to increased cytokine secretion may contribute to persistent chronic activation of pancreatic stellate cells, resulting in pancreatic fibrosis and chronic pancreatitis [13–16].

The pathogenesis of pancreatic pain is poorly understood and several theories have been proposed to explain pain in chronic pancreatitis.

2.1. Elevated pressure

One of the most controversial theories focuses on ductal hypertension. This theory builds on the observation that intraoperative and endoscopic measurements reveal high intraductal pressure in chronic pancreatitis. Morphological changes of the pancreas, such as ductal strictures or obstruction by stones, are thought to contribute to intraductal hypertension.

Stenosis of the common bile duct has been considered a possible cause of chronic pancreatitis pain. However, this has been refuted by a recent investigation finding neither influence of common bile duct obstruction on pain intensity nor effects of successful endoscopic drainage of biliary obstruction on pain pattern in chronic pancreatitis patients [17]. Along the same line, it has been hypothesised that sphincter of Oddi dysfunction may affect intrapancreatic ductal pressure, but this has not been supported by experimental data [18]. An investigation in 263 patients with abdominal pain, acute recurrent pancreatitis or chronic pancreatitis suggested that sphincter of Oddi dysfunction increases intrapancreatic ductal pressure in chronic pancreatitis. However, similar changes were also seen in acute pancreatitis and in patients with recurrent abdominal pain. There was no correlation between intrapancreatic ductal pressure and chronic pancreatitis severity [18]. Despite the fact that experimental data are lacking, presence of pancreatic duct stricture or obstruction due to fibrosis or stones causing pancreatic duct hypertension and dilatation remains one of the most widely accepted theories for causing pain in chronic pancreatitis [19].

Elevated pressure in the pancreatic parenchyma (a form of ‘compartment syndrome’) might be another factor in the pathogenesis of pancreatic pain. High interstitial pressure increases vascular resistance and reduces pancreatic blood flow. A number of studies have focused on evaluating the association between pancreatic fluid tissue pressure and pain in patients undergoing surgical drainage procedures for chronic pancreatitis. Increased tissue pressures have been recorded in these patients, with a significant correlation between pressure and pain [19].

2.2. Oxidative stress

There is growing recognition that an imbalance between reactive oxygen species (ROS) producing and ROS scavenging processes leads to the damage of pancreatic acinar cells, initiating auto-digestion of the entire pancreas. According to this theory, pancreatic pain is caused by the release of excessive amounts of oxygen-derived free radicals by alcohol, smoking and toxic chemicals, resulting in an inflammatory response and tissue damage [20]. Polymorphonuclear neutrophils of patients with alcohol-related chronic pancreatitis

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