

A New Perspective for the Medical Treatment of Intractable Pain in Chronic Pancreatitis Patients

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There have been many advances in understanding the pathogenesis and pathophysiology of chronic pancreatitis, but it remains an enigmatic disease with an unpredictable clinical course, and its treatment is not well standardized. The clinical course of the disease is characterized by frequent painful episodes in the early stages of the disease and then, over time, the pain attacks decrease in frequency and intensity in parallel with the progressive destruction of the gland. The pain tends to disappear during the natural course of the disease (the so-called "burn-out" phenomenon) or after a period of time (from a few years to a maximum of 10 years from the onset of the disease), and the destruction of the gland is clinically evident with the appearance of steatorrhea and diabetes. [1]. The pain significantly decreases the quality of life of chronic pancreatitis patients and sometimes leads to severe malnutrition [2, 3]. Based on data emerging from the Italian multicenter study on chronic pancreatitis [4], the typical profile of a patient with chronic pancreatitis is that of a male of about 40 years of age, with moderate pain intensity, located in the epigastrium and radiating to the back, independent of food intake and lasting less than one day. Of course, there is a small percentage of patients who have persistent abdominal pain and this group of subjects represents a therapeutic challenge.

In the course of chronic pancreatitis, the pain can be due to pancreatic and extra-pancreatic causes. The extrapancreatic causes are mainly related to the duodenal stenosis associated or not with stenosis of the main biliary duct [5]. Regarding the pancreatic causes of pain, recent studies [6, 7] have shown a neuropathic origin of this symptom, i.e. normal pain signals in the

presence of injury or disease of the peripheral and/or central nervous system. This is supported by Drewes *et al.* [7] who evaluated electroencephalography in chronic pancreatitis patients having pain. In these subjects, an increase in theta wave activity had been found and this seemed to be a marker of neuropathic pain. Furthermore, it is also known that, in the pancreatic tissue of patients with chronic pancreatitis, there is an increase in the number and diameter of nerve fibers [8]. The chronic inflammatory process produces a massive release of local lytic enzymes which leads to the release of several pro-inflammatory cytokines and pro-fibrotic agents, such as TGF-beta1 and growth factor B derived from platelets and capable of inducing fibrosis. As result of this process, there is also a mechanism of neurogenic inflammation mediated by transient receptor potential vanilloid-1 (TRPV-1) [9, 10]. Other receptors involved in this process are the calcium channels of T-type (located on sensory intrapancreatic fibers) activated by hydrogen-sulfide. The activation of peripheral nerve fibers determines the synthesis of substance P; the synthesis of substance P is also increased by protein 43 that is overexpressed in chronic alcoholic pancreatitis. Substance P carries out many activities [11]: it stimulates inflammatory cells to produce cytokines through the neurokinin 1 receptor; it increases polymorphonuclear cells, macrophages and fibroblasts locally and induces nerve regeneration, and it also causes a vasoconstriction of arterioles determining ischemia of the nervous fibers themselves. Moreover, the pain in chronic pancreatitis is the result of the effect of somatic and visceral fibers which result in changes in neurons [12]. This phenomenon leads to an hyperalgesia mediated by the central nervous system even in the absence of a peripheral nociceptive stimulus. This mechanism is associated with a functional rearrangement of the cerebral cortex which leads to a "pain memory" over time and independent of the peripheral input [13].

The persistence of pancreatic pain leads to surgery in 11% of patients and to endoscopic treatment in

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approximately 29% of patients [4]. After surgical treatment, the disappearance of pain, or at least its substantial reduction, is observed in 67-94% in the short term whereas good results are achieved in 50-88% of the subjects over a long-term period [14]. Thus, for many patients, we need adequate medical treatment, especially for those patients who do not benefit from surgical or endoscopic approaches. The traditional medical approach is based on the administration of long-acting octreotide, tricyclic antidepressants, narcotics or a celiac plexus nerve block using computed tomography or ecoendoscopy. For this reason, studies exploring additional techniques for alleviating pain in chronic pancreatitis patients are welcome. Thus, it is worth reporting the study of Kongkam *et al.* who have evaluated the efficacy of the intrathecal narcotics pump [15]. They studied 13 patients who had experienced intractable upper abdominal pain from CP. Each patient had multiple other failed treatment modalities, including partial pancreatic resections in 6 patients. They were offered an intrathecal narcotics pump after a successful intraspinal opioid trial. The etiology of chronic pancreatitis was unknown in 3 subjects, due to cystic fibrosis in 2 and due to alcohol abuse in 2; pancreas divisum was present in the remaining 6 patients. The median duration of severe, intractable pain prior to the intrathecal narcotics pump was 6 years and the median follow-up time after the intrathecal narcotics pump was 29 months. The intrathecal narcotics pump was *in situ* for a mean duration of 29 months. Seven patients had a pump exchange or removal for various reasons, such as improvement of pain, meningitis, meningitis with subsequent replacement or pump failure. The mean pain score prior to implantation was significantly higher than that calculated one year after entry into the study. The median oral narcotic dose before and one year after the intrathecal narcotics pump were morphine sulfate equivalents 337.5 mg/day and 40 mg/day, respectively ($P < 0.01$). Two patients were considered failures as they still required a high dosage of both oral and intrathecal medications to control their pain, despite significant pain-score improvement; one patient who was excluded due to meningitis was also considered a failure. Therefore, the overall success rate of the intrathecal narcotics pump based on an intention-to-treat analysis was 76.9%. The major complications of the intrathecal narcotics pump observed in 3 patients (23.1%) were central nervous system infection requiring pump removal, cerebrospinal fluid leak requiring laminectomy and perispinal abscess with bacterial meningitis requiring pump removal. This study shows the efficacy of the intrathecal narcotics pump in chronic pancreatitis patients with persistent pain; however, as previously reported [16], the risk of this therapeutic modality is high. Furthermore, we need a longer follow-up and especially therapeutic trials comparing pancreatectomy, the intrathecal narcotics pump and implanted nerve stimulators.

Conflict of interest The authors have no potential conflicts of interest

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