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Dopaminergic Drugs to Relieve Pain from Chronic Pancreatitis- A Novel Therapy

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ABSTRACT

Purpose: *To describe a highly effective novel treatment for relieving pain from chronic pancreatitis even when high potency long-acting opioids fail to improve pain.*

Methods: *Dextroamphetamine sulfate slowly titrated to achieve the closure to a tolerable dosage that relieved severe abdominal pain was given to a 50-year-old male suffering from chronic pancreatitis that failed to respond to all medical therapies including high potency opioids.*

Results: *After one year with marked improvement of severe abdominal pain, at a dosage of 90 mg amphetamine salts (56.4 ng dextroamphetamine sulfate), he was almost pain free with only occasional use of amphetamines. Most importantly he was completely off all other medication for pain including his high dosage opioids.*

Conclusion: *Though dextroamphetamine sulfate has been reported to ameliorate various types of abdominal pain, and pain in other areas of the body, even when standard therapies fail, this is the first reported case of marked abrogation of pain from chronic pancreatitis. The hypothesized medicine is that dextroamphetamine release dopamine from sympathetic nerve fibers, which in turn diminishes cellular permeability, and thus inhibits absorption of irritants into pancreatic tissue causing inflammation and pain.*

Keywords

Dopaminergic drugs, Symptomatic amine, Chronic pancreatitis, Cellular permeability.

Introduction

Approximately 80% of patients with chronic pancreatitis suffer with abdominal pain (typically epigastric with radiation to the back) which frequently is constant and very debilitating [1]. The etiology of the pain is believed to be caused by either pancreatic duct obstruction (which if the sole cause of pain could lead to intermittent rather than constant pain) or to acinar cell injury which tends to be more constant [2].

Unfortunately, treatment to relieve pain from chronic pancreatitis has not been very effective. One somewhat less invasive treatment for pain relief involves endoscopic surgery to remove stones that are obstructing and thus causing dilation of the pancreatic duct, or intraductal or extracorporeal shock wave lithotripsy [3]. Endoscopic surgery is best suited for those patients who are not considered good candidates for major surgery [3].

Major surgical procedures e.g., pancreaticoduodenectomy (Whipple procedure) or pancreatico- jejunostomy result in a better chance of pain relief than endoscopic procedures [4]. Unfortunately, even these major surgical procedures do not provide significant long lasting pain relief in the majority of cases, and thus are unable to prevent dependence on narcotics [5]. These major surgical procedures are aimed at still leaving intact functional islet cells of the pancreas to prevent very labile and difficult to control diabetes mellitus. However, sometimes that pain is so severe

that total pancreatectomy is required. However, to try to avoid controlling diabetes mellitus, the surgeon will eventually perform islet cell transplantation [6].

Total pancreatectomy may be sometimes required for patients with chronic pancreatitis. Total pancreatectomy leads to difficult subsequent management of replacing the exocrine and endocrine function of the pancreas but may be worth it to ameliorate the pain. What is interesting is that frequently the pain persists despite the total pancreatectomy. A possible explanation of the etiology of persistent pain in these circumstances has been suggested by Olesen et al. and is referred to as pain-associated adaptive cortical reorganization [7].

Conservative surgical therapies seem to have possible mild to moderate benefit for only those types of chronic pancreatitis with ductal obstruction. If one wants to avoid total pancreatectomy (with its complications and without necessarily significantly diminishing abdominal pain) the only option is medical with the use of medications strictly geared toward relieving pain.

Some studies have suggested some modest reduction in pain by the use of antioxidants to reduce oxidative stress, (which contributes to pancreatic tissue damage) e.g., vitamins A, C, and E and also methionine and selenium [8]. However, other studies fail to confirm beneficial effects of antioxidants [9]. Some mild benefit to pain from chronic pancreatitis was found with treatment with pregabalin [10]. Nevertheless, the majority of non-surgical candidates are treated by analgesics alone. The World Health Organization suggest a stepwise progression of first using non-steroid anti-inflammatory drugs, then low-potency opioids, and lastly higher potency and long-acting opioids.

The case reported here introduces a novel treatment option of using dopaminergic drugs for treating chronic pancreatis and, at least in the case presented, showed a marked reduction in abdominal pain.

Case Report

A 50-year-old male presented with severe constant mid-epistatic pain radiating to the back and left rib cage. Subsequent studies concluded that the pain was solely from idiopathic chronic pancreatitis without ductal dilatation. He did not respond to pregabalin and for the last three years he has been taking high dosages of long-acting opioids. Upon his initial presentation to our office, he had been taking morphine sulfate, 30mg extended-release tablet daily, oxycodone 10mg tablet 3x/day, and hydromorphone tablet 4mg 3x/day. Despite these high dosages of opioids, he was in constant pain, and over the last three years, he had lost over 50 pounds. He was 69 inches tall and weighed 118 pounds. He sought our opinion because he witnessed marked improvement of his wife's fibromyalgia and pelvic pain, following treatment with the dopaminergic drug dextroamphetamine sulfate. He was hoping this drug would provide him with some palliative benefits as well.

We explained to him that we have never treated a case of chronic pancreatitis before. However, we have witnessed marked relief of severe abdominal pain of various etiologies in both men and women, many of which markedly improved in a short time despite its long-term presence following treatment with the dopaminergic drug dextroamphetamine sulfate [11-13].

He gradually worked his way up to 90mg amphetamine salts immediate release tablets (56.4mg dextroamphetamine sulfate) starting at 15mg upon arising and at noon. He reported that after one year of treatment, with gradual improvement since the second week of treatment with dextroamphetamine sulfate, he is no longer taking any oxycodone, OxyContin or fentanyl and reported that he did not have any abdominal pain at all. When he has some mild abdominal pain, it is abated by acetaminophen. He gained 20 pounds that following year. He reports no side effects from taking dextroamphetamine sulfate.

Discussion

Based on evidence that the fetal-placental unit needs to create an increase in a cellular immune reaction to cause autoimmune removal of the thick cellular walls of some of the uterine arteries to create thin-walled spiral arteries which allows nutrient exchange between mother and fetus, it was hypothesized that an exaggeration of this inflammatory response could lead to pelvic pain and immune rejection of the fetal semi-allograft [14,15]. Part of the hypothesized model to explain this increased cellular response was that progesterone blocked the biogenic amine dopamine, and one of the functions of dopamine is to diminish cellular permeability allowing irritants to permeate the endometrium causing the needed inflammatory response [14,15].

If this model was correct, then theoretically dopaminergic drugs could diminish excessive permeability, and thus reduce pelvic pain and possible pain in other areas of the body. We decided to try such a drug for severe esophageal pain and did find marked improvement after treating with the dopaminergic drug dextroamphetamine sulfate. There were three choices of dopaminergic drugs at that time: levodopa, dextroamphetamine sulfate, and bromocriptine. We eliminated levodopa because of potential side effects but chose dextroamphetamine sulfate because it had been shown to also improve idiopathic edema, which was another one of the patient's clinical complaints [16-18]. This patients' pain related to achalasia responded very well to dextroamphetamine sulfate, but returned quickly whenever she decided to stop the drug to see if the condition was still present [19]. We first tried this on esophageal pain before trying it on pelvic pain even though the model was based on the fetal-placental unit and how successful implantation takes place. Subsequently, it was found that dextroamphetamine sulfate can efficiently relieve various types of pelvic pain, e.g., chronic pelvic pain, dysmenorrhea whether unexplained, or associated with endometriosis, dyspareunia, vulvodynia, adenomyosis, or pelvic pain of bladder origin [20-27].

Supporting the concept that the improvement is related to the release of dopamine from sympathetic nerve fibers, thus reducing permeability of a given tissue, and thus limiting infiltration of inflammatory agents, is the fact that levodopa when given to

women with Parkinson's disease corrected pain from vulvodynia in 100% of the cases [28]. Furthermore, severe chronic pelvic pain and dysmenorrhea have been improved by treatment with cabergoline [29].

Various types of abdominal pain have been reported to improve following treatment with dextroamphetamine sulfate e.g., long-term chronic unremitting abdominal pain of unknown origin [30]. Dextroamphetamine sulfate has shown drastic improvement of abdominal pain related to inflammatory bowel disease without pelvic pain, while at the same time markedly improving diarrhea [31-33]. Dopaminergic drugs have also markedly improved abdominal pain from conditions associated with smooth muscle dysfunction e.g., pathologic constipation, gastroparesis and pseudo intestinal obstruction [34-37]. This drug also completely revitalized a moribund young woman with autoimmune hepatitis [38].

Chronic pancreatis is uncommon with an estimated prevalence of 35-50 cases per 100,000 adults [39]. Thus, it would be almost impossible to perform a randomized controlled study or to evaluate a large series to determine the efficacy of dopaminergic drugs for chronic pancreatitis. At best, we can hope that this case report will influence other treating physicians to try a dopaminergic drug, e.g., dextroamphetamine, in patients suffering from chronic pancreatitis and publish their findings in other case reports. It will be especially interesting to see if dopaminergic drugs can thwart the progression of pancreatic damage, and thus inhibit morbidity beyond pain e.g., developing labile diabetes or complications of inhibiting pancreatic exocrine gland function.

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