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CASE REPORT

# Cannabinoid-Induced Pancreatitis: A Case Series

**Kurt A Wargo[1], Bridget N Geveden[1], Victoria J McConnell[2]**

[1]Auburn University Harrison School of Pharmacy. Auburn, AL, USA.
[2]Department of Internal Medicine, Huntsville Regional Medical Campus, University of Alabama-Birmingham School of Medicine. Huntsville, AL, USA

## ABSTRACT

**Context** There is only one previously published case report of acute pancreatitis secondary to the use of tetrahydrocannabinoid. While drugs, in general, account for 2% of all the causes of acute pancreatitis, we add to the literature three additional cases of cannabis-induced pancreatitis.

**Cases** The first case occurred in a 22-year-old man who admitted to smoking tetrahydrocannabinoid heavily over the days prior to admission. The second case involved a 23-year-old man with multiple admissions for tetrahydrocannabinoid-induced pancreatitis. The third case involved a 20-year-old female who admitted to smoking tetrahydrocannabinoid heavily over a period of two weeks prior to admission. In all cases, other causes of pancreatitis were ruled out. Furthermore, the symptoms associated with the acute pancreatitis subsided upon discontinuation of the drug.

**Conclusion** Cannabis is the world's most popular illicit drug with over 4% of the world's population using it each year. Despite this, acute pancreatitis is a rarely reported adverse effect of cannabis use. This case series adds to the literature that cannabis does in fact cause pancreatitis and it may be dose related, although the exact mechanism remains unknown.

## INTRODUCTION

According to the National Institute of Diabetes and Digestive and Kidney Diseases, the incidence of acute pancreatitis in the United States is approximately 17 new cases per 100,000 people per year [1]. Although acute pancreatitis has many known causes including biliary tract disease, ethanol abuse, and infection, medication-induced pancreatitis is a rare cause, only accounting for approximately 2% of all cases of pancreatitis [2]. The most frequently implicated medications are metronidazole, tetracycline, azathioprine, furosemide, thiazide diuretics, angiotensin converting enzyme inhibitors, didanosine, aspirin, valproic acid, and codeine [2]. An even rarer cause that has been implicated recently in the literature is illicit drug use, specifically, tetrahydrocannabinol (THC) [3]. To date, there has only been one reported case of THC-induced pancreatitis. While the exact mechanism for this adverse reaction remains unclear, it has been suggested that this effect may be dose-related [3]. We report three cases of possible THC-induced pancreatitis to add to the literature, two of possible dose related, the other of chronic use.

## CASE REPORTS

### Case 1

A 22-year-old African American male presented to the Emergency Department of our institution with a 5-day history of upper

abdominal pain with nausea, but no vomiting or diarrhea. The abdominal pain was described as constant, sharp in character, aggravated by movement and relieved by lying still. The pain was also described as radiating to the back, between the scapulae. He denied any past medical history and took no chronic medications. The patient admitted to smoking half a pack of cigarettes a day and drinking only occasionally. He initially denied any illicit drug use. Upon examination, the patient was afebrile, blood pressure was 133/80 mmHg, heart rate was 80/minute, and respiratory rate was 20/minute. The only positive finding upon examination was mild epigastric tenderness and hypoactive bowel sounds. Laboratory evaluation was only positive for a mildly elevated white blood cell count of 16,810 $mm^{-3}$ (reference range: 5,000-10,000 $mm^{-3}$) with a differential of 68% neutrophils (reference range: 55-70%) and 22% lymphocytes (reference range: 20-40%), but no immature bands. Lipase and amylase were elevated at 399 U/L (reference range: 0-60 U/L) and 199 U/L (reference range: 28-100 U/L), respectively. Alcohol level was negative, triglycerides were 68 mg/dL (reference range: 0-150 U/L), and serum calcium was 9.6 mg/dL (reference range: 9.5-10.5 U/L). Ultrasound of the abdomen showed mild pancreatitis without gallstones or gallbladder wall thickening. Although a urine drug screen was not done, the following day, the patient admitted to smoking THC "heavily" over the past few days. He also admitted that a similar event occurred a year prior to this event, for which he was seen and discharged in the Emergency Department. Review of those medical records revealed an elevated lipase and amylase of 461 U/L and 206 U/L, respectively; however no urine drug screen was done at that time. He was advised to avoid THC and has not been admitted since. When performing the Naranjo algorithm for assessing probability of an adverse drug reaction, the patient was considered to have "probable" pancreatitis secondary to THC [4].

**Case 2**

A 23-year-old Caucasian male presented to the Emergency Department of our institution with complaints of sharp abdominal pain in the left upper quadrant-epigastric area that radiated to the back that had no aggravating or alleviating factors, for the past 2 days. The patient has a history of multiple episodes of pancreatitis for which he had a laparoscopic cholecystectomy in 2004. His only medications were clonazepam and pantoprazole. He admitted to smoking half a pack to one pack per day of cigarettes for the past three years, he denied alcohol use, but admitted to smoking THC, although did not elicit the degree to which he smoked. Upon physical examination he was afebrile with a blood pressure of 151/88 mmHg, heart rate of 90/minute, and respiratory rate of 21/minute. The only positive finding upon review of systems was diffuse abdominal tenderness, mostly in the left upper quadrant, with guarding, yet no rebound tenderness. Laboratory evaluation was positive for white blood cells of 17,000 $mm^{-3}$ with 85% neutrophils, 6% lymphocytes, and no immature bands. Lipase and amylase were elevated at 865 U/L and 532 U/L, respectively. Triglycerides were 65 mg/dL, serum calcium was 9.4 mg/dL, alcohol level was negative and urine drug screen was positive for benzodiazepines and THC. Ultrasound of the abdomen was negative, however, follow-up CT scan revealed mild pancreatitis with no biliary dilation. Upon review of old records it was noted that since 2002 the patient had been admitted or seen in the Emergency Department a total of 10 times for similar complaints and laboratory findings. Urine drug screen was performed 6 out of the 10 times and was positive for THC on each occasion. When performing the Naranjo algorithm for assessing probability of an adverse drug reaction, this patient was also considered to have "probable" pancreatitis secondary to THC [4].

**Case 3**

A 20-year-old Caucasian female presented to the Emergency Department with complaints of sharp abdominal pain in the left upper quadrant that radiated to the back for the past 24 hours and was associated with nausea,

vomiting, and watery diarrhea. She denied any past medical history and took no chronic medications. The patient admitted to "lightly" smoking marijuana over the past two years, however recently began smoking 2-4 cigarettes per day over the past two weeks. She denied alcohol use. Upon examination, the patient was afebrile, blood pressure was 126/84 mmHg, heart rate was 75/minute, and respiratory rate was 18/minute. The only positive finding upon examination was mild left upper quadrant tenderness upon palpation. Laboratory evaluation was only positive for an elevated BUN/creatinine ratio of 20 (reference range: 10-15), and mild hypokalemia (3.3 mEq/L; reference range: 3.5-5.0 mEq/L)). Lipase was elevated at 515 U/L (reference range: 0-60 U/L). Alcohol level was negative, triglycerides were 64 mg/dL (reference range: 0-150 mg/dL), and serum calcium was 9.3 mg/dL (reference range: 9.5-10.5 mg/dL). Human chorionic gonadotropin was negative. Ultrasound of the abdomen showed mild pancreatitis without gallstones or gallbladder wall thickening. Urine drug screen was only positive for THC. When performing the Naranjo algorithm for assessing probability of an adverse drug reaction, the patient was also considered to have "probable" pancreatitis secondary to THC [4]. She was discharged and counseled to avoid the use of marijuana in the future.

## DISCUSSION

According to the United Nations Office of Drugs and Crime 2006 World Drug Report, over 166 million people worldwide consume cannabis each year, which is approximately 4% of the world's population, making it the most popular illicit drug [5]. There are clear ramifications associated with long-term cannabis use including infertility, erectile dysfunction, visual disorders, and schizophrenia; however, pancreatitis is one of the least reported/recognized complications of this drug [3].

Although the exact mechanism for acute pancreatitis secondary to THC is unknown, one possible mechanism is through agonism of the cannabinoid type I (CB1) receptor. There are two known cannabinoid receptors in humans, CB1 and CB2. The CB1 receptor is mainly expressed in the central nervous system, endothelial cells, and smooth muscle cells of blood vessels [6]. The CB2 receptors are mainly located in immune cells, but are also found in the brain, cirrhotic liver, and bone [7]. Interestingly, both receptors have been found in the pancreas, and their antagonism may contribute to the regulation of metabolism through decreased insulin resistance, regulation of appetite, and decreased weight in obesity [8].

In an experimental study using murine models with mild and severe acute pancreatitis, it was observed that significantly higher levels of anandamide, an endogenous cannabinoid, were present in severe versus mild pancreatitis and contributed to worsening on the condition [6]. When the rats were administered a CB1 receptor antagonist, mean arterial pressure and survival was improved in those with severe, rather than mild, pancreatitis. Therefore, theoretically, exogenous THC, which has similar pharmacological actions as anandamide, could elicit a similar response of worsening pancreatitis through agonism of the CB1 receptor. However, if this were true, pancreatitis would already have to be present and a patient would have to consume THC during the time of the episode, unless, the dose of THC was high enough to elicit an acute attack on its own, which has not been demonstrated to date.

To further confuse the picture, a recent study using both human and murine models with acute pancreatitis demonstrated beneficial effects of the endogenous cannabinoid system, decreasing the associated inflammation and pain [9]. Furthermore, addition of an exogenous CB1 and CB2 agonist significantly decreased inflammation and pain associated with acute pancreatitis, suggesting a potential therapeutic use for such agents in the future.

It is the hope of these authors that the issues can be clarified in the laboratory setting, using exogenous cannabinoids in an attempt to induce pancreatitis.

Another area of interest is in the possibility that marijuana played only a minor role in the above cases and perhaps the major cause of pancreatitis was secondary to sphincter of Oddi dysfunction and microlithiasis. In this theory, gallstones that travel through the biliary tract may lead to functional stenosis of the sphincter of Oddi through fibrosis and anatomical obstruction (type I sphincter of Oddi dysfunction) or functional obstruction (type II and type III sphincter of Oddi dysfunction) [10]. In a study of 85 patients with unexplained abdominal pain of pancreatobiliary origin, only 3.5% had microlithiasis, making it a rare cause of sphincter of Oddi dysfunction [10]. In another study of 60 patients status/post cholecystectomy with recurrent biliary pain found that only three patients had cholesterol crystals and none had bilirubinate crystals, suggesting that the presence of microlithiasis plays no role in sphincter of Oddi dysfunction [11]. While it is unlikely that microlithiasis played a role in the development of pancreatitis in the above patients, other causes of sphincter of Oddi dysfunction could have been ruled out by endoscopic retrograde cholangiopancreatography, which was only shown to be negative in Patient #2.

## CONCLUSIONS

In all three cases described, other causes of pancreatitis were ruled out. None of the patients had significant alcohol use, nor were there family histories of pancreatitis. Cholelithiasis was not present and triglyceride levels were normal. Furthermore, the patients described were not receiving any medications known to cause pancreatitis. Although the exact mechanism remains a mystery, THC use should be considered a risk factor for the development of acute pancreatitis.

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**Keywords** Cannabinoids; Cannabis; Marijuana Abuse; Marijuana Smoking; Pancreatitis

**Abbreviations** CB: cannabinoid receptor; THC: tetrahydrocannabinoid

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**Correspondence**
Kurt A Wargo
301 Governors Dr.
Huntsville, AL
USA 35801-5123
Phone: -1-256.551.4538
Fax: +1-256.551-4542
E-mail: wargoka@auburn.edu

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