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PAIN MANAGEMENT (S MACE, SECTION EDITOR)

Cannabinoid Hyperemesis Syndrome

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Abstract

Purpose of Review This review describes the clinical presentation and treatment for cannabinoid hyperemesis syndrome (CHS). Typical treatment for nausea, vomiting, and abdominal pain may not be effective in patients with CHS. Alternative treatments have been suggested.

Recent Findings The pathophysiology of CHS may be due to dysregulation of the endocannabinoid system. Two cannabinoid receptors (CB1, CB2) have been identified. Theories proposed to explain CHS including chronic stimulation of the CB1 receptor, binding of the CB1 receptor causing decreased gut motility, desensitization of CB1 receptors (these CB1 receptors generally have antiemetic effects), or interaction of the TRVP-1 receptor with the ennocannabinoid system.

Summary CHS should be in the differential diagnosis for any patient with nausea, vomiting, and abdominal pain. The usual treatment for nausea, vomiting, and abdominal pain may not be effective for patients with CHS. Other newer, off-label treatments for CHS have been proposed.

Keywords Cannabinoid hyperemesis syndrome · CHS · Chronic abdominal pain · Chronic marijuana use and vomiting, hot shower for vomiting control, capsaicin for CHS, haloperidol for CHS

Introduction

Cannabis has a long history linking to many cultures; its use has been dated back many millennia. Although it was categorized as an illegal substance via the Marijuana Tax Act of 1937, marijuana today is the most used illicit drug according to the 2015 National Survey on Drug Use and Health [1]. The Controlled Substances Act of 1970 classified cannabis and its cannabinoids as a schedule 1 substance, meaning cannabis has been determined to have a high potential for abuse and having no accepted medical use. There are, however, two synthesized cannabinoids that the Food and Drug Administration (FDA) has approved as medications in 1985, dronabinol (Marinol) and nabilone (Cesamet) [1]. Both of these medications are not schedule 1 drugs and are used primarily to treat chemotherapy-induced nausea and vomiting.

Cannabis has been used therapeutically for multiple other medical conditions as well. However, as a schedule 1 drug, cannabis availability for research and academic purposes is severely limited, making quality evidence-based data difficult to establish. Cannabis and/or cannabinoid agents have been used to treat chronic non-cancer pain, with a review of 15 of 18 trials demonstrating analgesic effects compared to placebo [2]. Cannabis has also been used to augment treatment for several neurological disorders, including peripheral neuropathy, muscle spasticity from MS, and epilepsy [3, 4]. In addition to its antiemetic properties, cannabis consumption creates appetite stimulation and has been used for cachexia as well as conditions such as AIDS, Parkinson's, and Alzheimer's, ALS, inflammatory bowel disease, and migraine/headaches [5, 6].

At the state level, various laws have been passed to decriminalize cannabis, allowing for different levels of medical and recreational use in at least 29 states [7]. As an unintended consequence of this, there exists a limited amount of cannabis-related research and evidence to treat an increasing number of patients seeking cannabis use–related health care. There is a data suggesting that states which have passed medical and recreational laws decriminalizing cannabis have also seen significant

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increases in cannabis-related emergency room visits [8]; a trend that seems to mirror more subtle national data as well [9].

Case Presentation

A 46-year-old woman presents to the Emergency Department with nausea, vomiting, and abdominal pain for 1 day. The pain and nausea are getting progressively worse. She admits to not taking her evening lantus last night and has had poor oral intake today. She has not taken her morning medications due to nausea and vomiting and complains of fatigue and thirst. She denies fever, chills, cough, dysuria, flank pain, diarrhea, and hematemesis. The patient was in her normal state of health until the morning of presentation, and the evening before she felt well and attended a party.

She has a past medical history of hypertension, type II diabetes, and polysubstance abuse. Medications include amlodipine 10 mg daily, insulin glargine 34 units subcutaneously at bedtime, short-acting insulin 4 units subcutaneously three times daily with meals, folic acid 1 mg daily, thiamine 100 mg daily, and acetaminophen 650 mg three times daily as needed for pain.

She is allergic to penicillin. Her social history is positive for smoking one pack per day, six glasses of wine per week, and drug use includes cocaine and marijuana. She is not married and sexually active, and she currently works as a parking attendant.

The patient appears in no acute distress upon examination with a blood pressure of 170/80, pulse of 70 beats per minute, respirations of 18 breaths per minute, temperature of 36.9 °C (98.2 °F), and an oxygen saturation of 99% on room air. Examination of her head, eyes, mouth, and neck were unremarkable. Cardiovascular and pulmonary examinations were normal. Abdominal exam was benign, with normal bowel sounds, no tenderness to palpation, no distention, no masses, no hepatosplenomegaly, and no rebound nor guarding. She is somewhat sleepy, however, exhibits no neurological deficits and was fully alert and oriented.

While the above results were pending, a bedside glucose reading revealed hyperglycemia (338 mg/dL) and she received 2 L of IV normal saline, ondansetron 4 mg IV, and insulin glargine 34 units subcutaneous plus regular insulin 6 units subcutaneous. Nausea improved slightly and her pain remained unchanged. She then admitted to smoking more marijuana than usual for the past several weeks and denied drinking heavily the night before. Additionally, she reported several prior episodes similar to this presentation in the past and denied having ever had diabetic ketoacidosis.

The patient's laboratory results showed a glucose of 353 mg/dL, Na of 136 mmol/L, BUN of 11 mg/dL, creatinine of 0.65 mg/dL, chloride of 95 mmol/L, a CO_2 of 26 mmol/L, and an anion gap of 15. She had a leukocytosis of 14.4 k/uL, a normal hemoglobin of 13.7 g/dL, and a serum lactate of 1.9 mmol/L. Her urinalysis was within normal limits with a specific gravity of 1.020, glucose 500 mg/dL, ketones 40 mg/dl, nitrite negative, leukocyte esterase, and no crystals seen on the microscopic evaluation. Urine pregnancy testing was negative, and ECG showed normal sinus rhythm at 76 beats per minute, no ectopy, normal QT, and no ST segment changes. Urine toxicology is positive for cocaine and cannabinoids, but negative for phencyclidine, benzodiazepines, amphetamines, opiates, and barbiturates. Serum ethanol is not detectable.

As she remained symptomatic, after the labs and ECG were reviewed, she received haloperidol 5 mg intramuscular and topical capsaicin to the abdominal wall. Repeat blood glucose was 220 mg/dL, and repeat serum lactate was 1.6 mmol/L. Her symptoms improved markedly; however, she was very anxious about being discharged prematurely. In addition, the time of day was 11:30 pm when her symptoms began to improve, so it was decided to admit her to the 23-h observation unit for further treatment.

In the observation unit, the patient received normal saline as a drip at 75 cc/h, haloperidol 2 mg IM every 6 h as needed for nausea, ondansetron 4 mg IV every 6 h as needed for nausea, and continued topical capsaicin 0.025% to the abdominal wall. Blood glucose levels were followed. In the morning, she resumed a diet, which was advanced, and she was discharged home in good condition.

Symptoms

Cannabinoid hyperemesis syndrome (CHS) refers to a constellation of symptoms that occur in the context of chronic cannabis use. These symptoms include nausea, vomiting, and sharp abdominal pains that are usually cyclic in nature and not diagnostically otherwise explained. A defining characteristic of this syndrome is a history of compulsive hot showers to help mitigate these symptoms. CHS has three distinct phases: prodromal, hyperemesis, and recovery phases [10]. The prodromal phase can last for long periods of time and is characterized by nausea, vomiting fears, and abdominal pain. The patient's food intake is usually unchanged during this phase. The hyperemesis phase includes paroxysms of intense, persistent, nausea and vomiting, and very sharp abdominal pains. This phase is the most frequent in which patients will seek medical care. Not only are the symptoms very undesirable, but the patient may be dehydrated, require electrolyte replacement, and experience acute weight loss. The recovery phase is the resolution of the symptoms, usually with the cessation of cannabis use. Patients will regain their weight as well as resume normal eating and bathing patterns [11].

Pathophysiology

The true pathophysiology of CHS is not fully defined, but it has been proposed to be related to the endocannabinoid system and resulting dysregulation. Two cannabinoid receptors (CB1 and CB2) have been identified as having roles in nausea, emesis, nociception, anxiety-related behaviors, and stress maladaptation [11]. It has been suggested that chronic stimulation of primarily the CB1 receptor contributes to CHS. Another theory suggests that binding of the CB1 receptor decreases gut motility and gastric emptying. It has also been proposed that chronic cannabis use leads to desensitization and down regulation of CB1 receptors that generally have antiemetic effects, causing the paradoxical nausea and vomiting symptoms of CHS [12]. There also is a theory suggesting at that another receptor known as the TRVP-1 receptor may interact with the endocannabinoid system as well [13, 14]. This receptor is the target of capsaicin, which is discussed later. Finally, in a theory not including receptors, it is postulated that THC causes splanchnic vasculature dilation, causing CHS. Overall, the grade of evidence of any of these theories is very low and, in some ways, helps to explain why multiple interventions may help with CHS management.

Treatment

There are multiple reports that indicate that standard interventions used for patients presenting with similar complaints such as intravenous fluids, ondansetron, dolasetron, prochlorperazine, promethazine, droperidol, dexamethasone, and metaclopromide are not adequate for resolution of symptoms in CHS [13–16, 17•, 18–19]. Alternative treatments such as benzodiazepines, haloperidol, and capsaicin may be more efficacious, though these are presently considered as an off-label use [15, 16, 17•,]. Antihistamines such as diphenhydramine, meclizine, and dimenhydrinate, as well as anticholinergics such as atropine and scopolamine, have been useful for treating nausea and vomiting associated with motion sickness. However, there is no evidence to suggest that either antihistamines or anticholinergics have been successfully used in treating CHS as single agents [20•].

Benzodiazepines, though addictive, have a long history and a variety of uses. Additionally, most clinicians are familiar with the use of benzodiazepines. These medications function as GABA receptor antagonists as well as possess inhibitory effects on medullary and vestibular nuclei associated with nausea and vomiting. Lorazepam is the most common benzodiazepine that has been reported to be used with a positive response in the treatment of CHS [20•, 21, 22]. Other benzodiazepines used in treating CHS include diazepam, alprazolam, clonazepam, and chlordiazepoxide [18–19, 20•, 23•, 24]. Though benzodiazepines have been safely administered in emergency departments for decades, the addiction potential for this class of medications should be considered when treating patients with CHS as many of these patients may have addiction issues that go beyond cannabis.

Haloperidol also has a long track record for treatment of acute psychosis or treatment of agitation in the Emergency Department [15, 22]. There is currently no FDA-approved indication for the use of haloperidol for the treatment of CHS. However, there are numerous publications citing the efficacy of intravenous haloperidol in the treatment of symptoms due to CHS [15, 16, , 19, 20•, 21, 22, 23•, 24]. The efficacy of haloperidol as an antiemetic in post-surgical and chemotherapy patients has also been reported [15, 23•]. Several papers indicate that haloperidol has been administered intravenously for treating CHS with a good response, though our patient received her dose intramuscularly. This difference in route of administration may account in part for the slow response to the medication in our patient [15, 20•, 24]. As haloperidol is likely to be readily available in most Emergency Departments, it is a reasonable first-line medication for patients with CHS.

Capsaicin is a chemical found in several varieties of chili peppers and is a unique treatment option with encouraging results in the treatment of CHS. Its chemical name is 8-methyl-N-vanillyl-6-noneamide, and it binds to transient receptor potential vanilloid-1 (TRPV-1) receptors, which are found in close proximity to cannabinoid 1 receptors (CB-1). This close proximity may account for its effect [20•, 21, 23•]. The application of capsaicin cream to the abdomen has been reported to improve symptoms [19, 20•, 21, 23•, 25–27]. While the application of a topical paste is typically to the abdominal wall, the chest, back, and extremities have also been sites used for this treatment with positive results [19, 23•, 25, 26]. Though historically capsaicin is not a medication that is readily available in many Emergency Departments, it is reasonable to consider adding it to the list of medications readily available to administer in the emergency department. This may become more important as CHS may likely become more recognized in patients presenting for emergency care.

Hot showering or bathing is well known to improve symptoms of CHS, so much so that this behavior is considered by many to be a criterion for the diagnosis, differentiating CHD from cyclic vomiting syndrome [17, 20•, 28]. Additionally, there have been studies in animal models that also demonstrate compulsive hot water bathing in rodents [29]. Several authors suggest that if patients are admitted to the hospital for treatment of CHS, that hot baths or showers be made available to the patient and for patients being discharged, that instruction for safe and frequent bathing practices at home be provided. Though efficacious, this is not a course of therapy that is easy to administer in the Emergency Department.

There are no controlled trials to evaluate the use of corticosteroids for treating the pain or nausea of CHS. However,

there are three articles in which corticosteroids were administered in combination with other agents without significant improvement in symptoms [20•, 28, 30]. Currently, there is no sufficient evidence to suggest using corticosteroids for patients with CHS in the Emergency Department.

Additional Treatment Considerations

Patients presenting to the Emergency Department with abdominal pain associated with CHS often request pain medication and may even request narcotic analgesics. It is well-known that nausea and vomiting are commonly seen with the use of opiates, and emergency physicians may be appropriately hesitant to order opiates for these patients. Numerous papers note the use of various opiates for treating pain associated with CHS, including morphine, hydromorphone, tramadol, fentanyl, and even methadone [20•, 24, 31]. There is no consensus on which agent or agents should be used; however, it is clear that careful consideration should be applied when opiates are used. Just like benzodiazepines, there may be addiction concerns for patients receiving narcotics, especially in those patients that have had multiple presentations for CHS and have been treated with opioids in the past.

It is not clear how prevalent the diagnosis of CHS is. Many patients present to Emergency Departments in the USA everyday with symptoms similar to CHS symptoms. However, emergency physicians may not always consider this entity or obtain the necessary historical features to suggest CHS. In addition to severe nausea and vomiting, abdominal pain is present 85% of the time, which alone leads to a very wide differential diagnosis [31]. However, a history of using cannabis for more than a year is present 75% of the time and weekly cannabis use is reported in 97% of patients [31]. Resolution after cessation of cannabis use is seen 97% of the time and hot bathing or showering helps relieves symptoms in 92% of cases [31].

Cessation of cannabis use results in resolution of CHS symptoms in nearly all patients [32]. Therefore, no treatment plan for a patient with CHS would be complete without a discussion regarding termination of use. One study which reviewed multiple, previously published reports notes that 84.2% of patients reported abstinence from marijuana after receiving treatment for CHS, and of these patients not continuing marijuana use, 86.4% reported resolution of CHS symptoms. In a team-based modality, the successful employment of a specialized addiction team to address the need for abstinence from cannabis in which 5 of 7 patients enrolled into the program achieved both abstinence as well as resolution of symptoms [33]. It is widely accepted that a good long-term prognosis can be expected in patients who achieve abstinence with symptom resolution [31, 32].

Conclusion

Cannabis hyperemesis syndrome has been first described in 2004, despite recreational marijuana use in the USA for nearly a century prior [1]. Due to increased decriminalization by multiple US states, there has been an increased awareness of cannabis-related disorders, including cannabinoid hyperemesis syndrome. This relatively new and often difficult to correctly identify diagnosis is still underdiagnosed more than a decade after it was first reported. Recognition of CHS as a possible differential diagnosis of patients presenting with abdominal pain, vomiting, and cannabis use will certainly improve our ability to diagnose and treat these patients more efficiently and effectively. Emergency physicians should include CHS in the differential diagnosis of patients presenting with cyclic vomiting, especially when the patient is less responsive to typical treatment modalities for abdominal pain and vomiting. Physicians should also consider treatments, such as benzodiazepines, haloperidol, and heat or topical capsaicin in these cases, especially when the patient reports a history of cannabis use. While these treatments may provide temporary relief for patients while in the acute care setting, cessation of cannabinoid use has been linked to complete resolution of CHS.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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