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Treatment of Cannabinoid Hyperemesis Syndrome-Associated Nausea with Haloperidol: A Case Report

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Abstract

Introduction: Because of the rising prevalence of cannabis abuse, cannabinoid hyperemesis syndrome (CHS) was recognized as a new medical diagnosis in 2004. Despite the syndrome's growing prevalence, many providers are unfamiliar with its diagnosis and treatment, and there is little data to back up clinical knowledge and treatment recommendations. For many years, haloperidol has been widely used as an antiemetic, despite a lack of evidence-based clinical data on efficacy and side effects. We present the case of a female who presented to the emergency room with suspected CHS and was treated with haloperidol. **Case:** A 34-year-old African-American woman with diabetes and a history of marijuana use presented to the emergency department with refractory nausea and vomiting. Her urine drug screen came back positive for THC, but she denied using marijuana prior to this admission. She stated that she was following her current medication regimen. She denied drinking alcohol and smoking cigarettes. Multiple doses of ondansetron, promethazine, scopolamine, and metoclopramide had no effect on the patient. After two days of treatment with haloperidol 5 mg by mouth every 8 hours, nausea and vomiting subsided. **Discussion:** Haloperidol was able to control nausea and vomiting in six previous case reports of CHS. However, haloperidol was administered intravenously in five of the reports, and the route of administration was not specified in the sixth. To the best of our knowledge, we are the first to demonstrate the benefit of oral haloperidol for CHS. **Conclusion:** Although cessation of marijuana use is required for long-term resolution of CHS, our case and six others show the benefit of using IV haloperidol for acute management and oral for relapse prevention. More extensive clinical trials are needed to confirm haloperidol's therapeutic role in patients presenting with CHS symptoms.

Keywords

Cannabinoid, Hyperemesis, Haloperidol, Marijuana, Case Report

1. Introduction

Cannabinoid hyperemesis syndrome (CHS) is associated with cannabinoid overuse. According to the United Nations, in 2017, an estimated 238 million people used cannabis in 2017, 22% percent of that total are users in North America, making it the most widely used drug globally [1]. Cannabis-induced adverse drug effects increased with its increased access [2] and in 2004, CHS was recognized as a new medical diagnosis [3].

CHS is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing to relieve symptoms [4]. The clinical characteristics and appearance can be divided into three phases: the prodromal phase, the hyper-emetic phase, and the recovery phase [5]. The prodromal phase can last months to years with recurrent symptoms of early morning nausea, fear of vomiting, and abdominal discomfort [6]. This phase also includes a normal eating pattern with increased use of cannabis to alleviate nausea. The hyper-emetic phase consists of persistent vomiting that could be debilitating with weight loss of up to 14 kilograms and compulsive warm bathing to relieve symptoms of nausea and cannabis vomiting. The recovery phase follows a complete halt to use, with a total resolution of symptoms within 12 hours to 3 weeks, a return of normal eating pattern, weight gain, and recurrent hot bathing habits [6].

The only definitive treatment identified for CHS is the cessation of marijuana [3] [5] [7] [8] [9]. Pharmacological treatment of CHS can be divided into two phases: therapy for the hyperemetic phase and relapse prevention. Patients may require hospitalization during the hyperemetic phase secondary to abdominal pain, dehydration, as well as severe nausea and vomiting. Supportive therapy serves as the mainstay of treatment during this phase [10]. There is limited literature available on haloperidol as the standard of care in CHS. However, haloperidol has been widely used as an antiemetic for many years and has been described to provide symptom relief in some patients with CHS [11]. This article presents the findings from a literature review on CHS. It discusses a female patient who was successfully treated for CHS with haloperidol given by mouth.

2. Case Report

A 34-year-old African American female presented to the emergency department with complaints of recurrent nausea and vomiting. Three days before admission, the patient reported having nausea and vomiting after smoking marijuana and was unable to keep any food down. The patient has had two previous admissions for the same symptoms. During those admissions, the patient was given on-

dansetron, metoclopramide, erythromycin, and promethazine with no relief of symptoms. The patient's past medical history included Type 1 diabetes mellitus, gastroparesis, and hypertension. Her social history was significant for daily marijuana use, but she denied alcohol and tobacco.

2.1. Clinical Findings

Upon the current admission, the patient denied chest pain, headaches, shortness of breath, back pain, and diarrhea. The patient also stated that nothing aggravated or relieved the symptoms. Vitals were as follows: Blood pressure 153/110 mmHg, Pulse 95 beats/min, temperature 98.9°F, respiratory rate 15 breaths/min, and SpO2 100% on room air. A physical exam revealed an alert, awake, and oriented female with dry mucus membranes, diffuse abdominal pain, and bilateral mild tingling sensation in lower extremities. Her vomiting was bilious and sometimes mixed with blood. Cardiac and lung examinations were unremarkable. The patient's social history, clinical presentation, vital signs, and labs at admission supported the diagnosis of CHS and are depicted in Table 1.

2.2. Therapeutic Intervention

Table 2 shows that the patient was unresponsive to promethazine 12.5 mg intramuscularly (IM) every 6 hours as needed and metoclopramide 10 mg IV × 1 dose during the hospital course. When given haloperidol 5 mg IM on hospital day #2, the vomiting subsided, but she was still nauseous. During the third day of therapy, the patient was given haloperidol 5 mg orally and felt better.

Table 1. Admission Laboratory Tests.

Serum Test	Value	Serum Test	Value
Sodium	138 mEq/l	Hemoglobin	10.5 g/dl
Potassium	3.3 mEq/l	Hematocrit	22 %
Chloride	108 mEq/l	WBC	9.4×10^9 per liter
Bicarbonate	26 mEq/l	Platelets	259×10^9 per liter
BUN	14 mg/dl	A1C	10.49%
Creatine	0.9 mg/dl		
Glucose	174 mg/dl		

Table 2. Cannabinoid hyperemesis syndrome treatment.

Hospital Day	Treatment	Outcome
#1	Promethazine 12.5 mg IV @ 2202 Metoclopramide 10 mg IV @ 2310	Emesis × 2
#2	Haloperidol 5 mg IM @ 1156 Haloperidol 5 mg IM @ 2018	↓ vomiting but still nauseous
#3	Haloperidol 5 mg PO @ 0900	Patient felt better and requested to leave against medical advice

2.3. Follow-Up and Outcomes

The patient left the hospital against medical advice and was discharged on haloperidol 5 mg by mouth every 8 hours. The patient was given instructions regarding the diagnosis, expectations, follow-up, and return precautions. Unfortunately, despite counseling, the patient was not amenable to cannabis cessation at that time. She was also counseled on the importance of therapy adherence and following up with her primary care physician.

3. Discussion

Reports of CHS in patients have increased over the years, despite the syndrome's increasing prevalence, many physicians are unfamiliar with its diagnosis and treatment [6]. This under-recognition may be due to the paradoxical use for the treatment of nausea and vomiting, the stigma associated with cannabis use, and the illegal status of cannabis in some areas leading to under-reporting of use. The frequency of emergency department visits and high hospital admission rates for CHS exemplify the difficulty in symptom management [4]. The lack of knowledge and treatment recommendations regarding CHS compounds this issue.

We report the first case of recurrent acute cannabinoid hyperemesis syndrome sucessfully treated with haloperidol given both intramuscularly and orally. The Naranjo adverse drug reaction probability scale was utilized to assess the probability that the hyperemesis was related to cannabinoid use, and a total score of 6 (probable) was obtained (**Table 3**) [12].

Diagnosis is determined through receiving a detailed medication history and a

Table 3. Naranjo adverse drug reaction probability scale.

Question	Answer	Score
1. Are there previous *conclusive* reports on this reaction?	Yes	+1
2. Did the adverse event occur after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued, or a *specific* antagonist was administered?	Yes	+1
4. Did the adverse reaction reappear when the drug was readministered?	Yes	+2
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	Yes	−1
6. Did the reaction reappear when a placebo was given?	Do not know/ not done	−1
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	No	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Do not know/ not done	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	Yes	+1
10. Was the adverse event confirmed by any objective evidence?	Yes	+1
Total Score	**6**	

comprehensive physical examination. In a recent systematic review conducted by Sorensen and colleagues, the following diagnostic characteristics and frequency of each were found: history of regular cannabis use for over one year (74.8%), severe nausea and vomiting (100%), vomiting that recurs in a cyclic pattern over months (100%), resolution of symptoms after stopping cannabis (96.8%), compulsive hot baths/showers with symptom relief (92.3%), male predominance (72.9%), abdominal pain (85.1%), at least weekly cannabis use (97.4%), history of daily cannabis use (76.6%), and age less than 50 at time of evaluation (100%) [10]. With >10 years of self-reported cannabis use, our patient experienced the following symptoms: severe nausea and vomiting that has recurred over many months in a cyclic pattern.

Haloperidol is a drug primarily used for sedation, behavioral agitation, and as an antipsychotic. However, haloperidol has been used as an antiemetic for years, particularly in the anesthesia, general surgery, and oncology literature [13]. Haloperidol is a butyrophenone antipsychotic that non-selectively blocks postsynaptic dopaminergic D2 receptors in the chemoreceptor trigger zone (CTZ) [13] [14]. The CTZ is located in the medulla oblongata and is exposed to toxins in the bloodstream, which triggers vomiting. The mechanism of action of haloperidol's antiemetic effects in CHS is unknown. The medication may decrease nausea and vomiting by blocking the dopamine receptors in the CTZ, thus reducing input to the medullary vomiting center. Early administration of haloperidol in acute episodes of CHS may reduce symptoms, minimize the time in the emergency room, and reduce the rate of hospital admissions [15].

There are six case reports using haloperidol as treatment for CHS. These reported cases have been summarized in **Table 4**. In 5 out of the 6 reported cases,haloperidol was given intramuscularly only [16] [17], and in one case, the route of administration was not provided [18]. Also, interestingly only one of the cases was a woman [18] and our case makes two. In a recent analysis synthesizing findings from case reports found that men were overwhelmingly more likely to be diagnosed with CHS relative to women (72.9% vs 27.1%) [4]. However, this sex discrepancy may reflect heavier cannabis use reported among men relative to women, rather than a sex-specific sensitivity to this adverse effect of cannabis [19]. More studies are warranted to research these findings.

The main point from these six cases was that patients continued to have refractory nausea and vomiting with standard antiemetics. However, once given doses of haloperidol, the patients experienced a clinically significant improvement in their symptoms. And like the other cases, our patient received a multitude of other antiemetics without the relief of symptoms and it was only when she was treated with IV haloperidol followed by oral did her symptoms subside.

Our report wasn't without limitations. During this admission the patient received only one dose of metoclopramide. The attending physician made this decision based on the fact that the first dose didn't relieve the patient's symptoms and in previous admissions for gastroparesis but before the CHS diagnosis

Table 4. Summary of case reports using haloperidol to treat cannabinoid hyperemesis syndrome[a].

Patient and Presentation (Reference number)	Cannabinoid Use	Labs and Diagnostics	Intervention	Patient Outcome
34-year-old man with epigastric pain, nausea, and vomiting for 4 days. History of similar symptoms every 2 to 3 months for approximately 10 years. (Gnanaraj *et al.* 2011, [8])	Daily cannabis use since 1992, with only short intervals of abstinence resulting in complete resolution of his vomiting.	Unremarkable diagnostic tests: 3 computed tomographic scans, esophagogastroduodenoscopy, and several specialty consults. Vitals: BP: 116/64 mmHg, HR 94 beats/min, RR 20 breaths/min, pulse Oxygen 97% on room air, temperature 98.4˚F.	Morphine 4 mg IV, OND 4 mg IV, 1 liter normal saline IV fluid bolus.	The previous therapies did not help symptoms, but when given haloperidol 5 mg IV, symptoms resolved within 1 hour. He exhibited no further vomiting during 8 hours of observation, tolerated oral fluids, and then discharged.
27-year-old man presents with vomiting and abdominal pain for 3 days. Patient reported 15 - 20 episodes of non-bloody, non-projectile, and non-bilious vomiting, which were alleviated partially by taking hot showers. (Inayat *et al.* 2017, [16])	Smoking at least five joints a day for approximately 10 years.	Normal vital signs. Toxicology screening positive for cannabis. Abdominal examination: soft, non-tender and non-distended abdomen. No rebound or tenderness and normal bowel sounds. Initial laboratory evaluation was unremarkable.	OND, lorazepam and IV fluids.	Severe hyperemesis persisted after 2 days of conventional antiemetic treatment. Given haloperidol 1 mg IV, the patient responded well with clinically significant improvement. His compulsive hot bathing and GI symptoms began to diminish following next two dosages of 2 mg IV haloperidol.
18-year-old woman with emesis consistently non-bloody and non-bilious. Symptoms were worse in the morning and relieved only by smoking marijuana. (Jones*et al.* 2016, [18])	History of smoking using cannabis 2 - 3 times per day for two years and unwilling to quit.	Initial physical exam was unremarkable and vital signs were within normal limits. BMP, LFTs, and CBC were all normal. Tested positive for cannabis while symptomatic.	Haloperidol 5 mg daily for symptom relief.	At the next visit, patient reported complete resolution of previous refractory nausea, vomiting, and abdominal pain within one day of starting treatment.
34-year-old man with previously diagnosed recurrent CHS arrived to the ED with vomiting for 4 days. (Witsil *et al.* 2017, [17])	Previously admitted to hospital 7 times for same issue.	Unremarkable diagnostic tests and several specialty consults.	Promethazine and OND 4 mg IV and IV fluids.	Given haloperidol 5 mg IV, and within 1 hour, symptoms resolved and was discharged home from the ED.
48-year-old man presented to the ED with vomiting for 2 days. (Witsil *et al.* 2017, [17])	Chronic cannabis use.	Multiple unremarkable workups over the past year for cyclical vomiting	MET, promethazine, OND 4 mg IV, chlorpromazine and IV fluids with no symptom relief.	Given haloperidol 5 mg IV; within 1 hour, his vomiting resolved and was discharged home within 8 hours.
22-year-old man arrived for treatment of cyclical vomiting (Witsil *et al.* 2017, [17])	Recurrent CHS diagnosed 2 years ago.	Not reported	MET, OND 4 mg IV, and IV fluids.	Initial ED treatment with OND 4 mg IV and IVF were unsuccessful. He was then given haloperidol 5 mg IV; within 2 hours, his vomiting resolved, and he was discharged home 6 hours later.
28-year-old man (Witsil *et al.* 2017, [17])	Not reported.	Nondiagnostic workups	OND, MET, chlorpromazine with no symptom relief.	His initial ED treatment included haloperidol 5 mg IV, diphenhydramine 25 mg IV, and IVF. Within 1 hour, improved, had no further episodes of vomiting, and was discharged from our ED 6 hours later.

[a]IV-intravenous, ED-emergency department, IVF-intravenous fluids, OND-ondansetron, MET-metoclopramide.

metoclo-pramide was effective, that this admission her nausea and vomiting were not due to gastroparesis. Another limitation to consider is that the patient had some confounding conditions such as uncontrolled diabetes with her last A1C being 10.5 and associated gastroparesis. Even with these confounders we believe our patient experienced CHS because none of the typical medications used to treat gastroparesis such as metoclopramide or erythromycin eliminated her symptoms.

4. Conclusion

Although cessation of marijuana use is required for long-term resolution of CHS, our case and six others show the benefit of using IV haloperidol for acute management and oral for relapse prevention. More extensive clinical trials are needed to confirm haloperidol's therapeutic role in patients presenting with CHS symptoms.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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