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Case Report
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A Case Report on Cannabinoid Hyperemesis Syndrome in Palliative Care: How Good Intentions Can Go Wrong

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Abstract

Mrs. X, a 70-year-old female who was residing in the palliative care unit with the diagnosis of lung cancer. She underwent a course of chemotherapy consisting of paclitaxel, docetaxel, and cisplatin. She presented with hair loss, sore mouth, and loss of appetite, diarrhea, neuralgia, nausea and vomiting which developed approximately five hours after chemotherapy.

Nabilone was used for the last five years to manage Mrs. X's neuralgia. As her cancer progressed, dosage of nabilone was incrementally increased from 0.5 mg to 2 mg to control her pain; however, it exacerbated refractory nausea and vomiting. Nabilone was discontinued seven weeks after administration due to suspicion of cannabinoid hyperemesis syndrome. Hot baths were attempted with temporary relief. Her pain became well controlled with opioids and adjuvants and there has been no recurrence of nausea and vomiting since the cessation of nabilone.

Successful recognition and management of cannabinoid hyperemesis syndrome is especially important in individuals with co-morbid disorders in order to avoid cannabis toxicity.

Keywords: Cannabis; Cannabinoid hyperemesis syndrome; Palliative care; Oncology; Nabilone

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Background

Cannabis is the most used recreational drug worldwide, and it continues to grow due to legalization in many countries [1]. Synthetic cannabinoids are commonly used to manage pain, nausea, and vomiting in palliative care [1,2]. Nabilone, sold under the brand name of Cesamet is a synthetic cannabinoid with therapeutic use as an antiemetic and an analgesic for neuropathic pain [3,4]. Nabilone mimics delta (9)-tetrahydrocannabinol, the primary psychoactive compound found in natural cannabis. Despite the current acceptance of nabilone as a treatment option for nausea and vomiting, there is a lack of data regarding the side effects of its prolonged use leading to possible toxicity due to accumulation, and as a result, exacerbation of nausea and vomiting rather than alleviation.

Current research has shown recurrent cases of nausea and vomiting with distinct pathogenesis associated with chronic cannabis use known as Cannabinoid Hyperemesis Syndrome (CHS) may lead to toxicity due to the accumulation of cannabinoids [2]. This is a result of ingesting high amounts of botanical cannabis. The condition can cause distress for the patients, in addition to repetitive hospitalizations, and impact the quality of life of the patients and the cost of healthcare [3]. CHS is a prevalent health problem, as cannabis is readily available, and the abuse rate potential is high. Currently, the rate of cannabis consumption has rapidly increased due to COVID-19 and long stretches of quarantine have facilitated an environment which has seen a spike in cannabis, alcohol and other drugs of abuse which were used to help with coping [4].

Finding effective antiemetic solutions for CHS have proven to be difficult due to the overlapping nature of the symptoms with other conditions such as malignancy, chemotherapy, cyclic vomiting syndrome, viral gastroenteritis, and bulimia nervosa [2]. This report aims to create awareness of the role of cannabis in the development of CHS.

Case Presentation

Mrs. X, a 70-year-old female who was residing in the palliative care unit with the diagnosis of lung cancer. She underwent a course of chemotherapy consisted of paclitaxel, docetaxel, and

cisplatin soon after the diagnosis, complicated by hair loss, sore mouth, and loss of appetite, diarrhea, neuralgia, and nausea and vomiting developed approximately five hours after chemotherapy. Nabilone was used for the last five years to manage Mrs. X's neuralgia, and then nausea and vomiting developed post-chemotherapy.

Mrs. X's past medical history is remarkable for long-standing dementia, depression, and coronary artery disease. Her medications included bupropion, bisoprolol, haldol, lorazepam, and domperidone. Previous admissions to the acute care unit were unsuccessful in controlling her nausea and vomiting, and only resulted in short term improvement. Chronic hot bathing was temporarily relieving Mrs. X's nausea and vomiting.

She was initially started on 0.5 mg of nabilone orally once a day. As her disease progressed, nabilone was titrated up to 1 mg orally once a day which were controlling her pain and later on nausea, and vomiting. Unfortunately, nausea and vomiting recurred and became unmanageable in the community, and as a result admission to the palliative care unit was requested. A trial of increasing nabilone to 2 mg orally once a day exacerbated refractory nausea and vomiting and led to cognitive decline, but she was confident that the therapeutic benefits of nabilone outweighed the potential harms. Nabilone was discontinued seven weeks after admission, and nausea and vomiting resolved, although pain escalated. Attempt to reinitiate nabilone to help with the pain led to more severe episodes of nausea and vomiting. CHS was suspected due to longstanding use of nabilone, and as a result she was switched to hydromorphone and gabapentin to control her pain, serotonin and norepinephrine reuptake inhibitors were later added to augment analgesia.

Differential diagnosis

Mrs. X's vomiting may have been multifactorial, related to the advanced stage of lung cancer and medications side effects (i.e., chemotherapy agents). Toxicity induced by drug-drug interactions with paclitaxel may have led to reduced renal clearance of nabilone, perpetuating nausea and vomiting. Alternatively, the stress of undergoing chemotherapy in advanced stage lung cancer combined with food deprivation could have contributed to further breakdown of her fat stores causing a mass release of delta (9)-tetrahydrocannabinol from years of nabilone use.

Cyclic vomiting syndrome is an important differential diagnosis to CHS. Both cyclic vomiting syndrome and CHS are characterized by recurrent episodes of heavy nausea, vomiting and abdominal pain, but cyclic vomiting syndrome usually co-occurs with mental health disorders such as depression, whereas CHS resolves with the cessation of marijuana use [5]. Mrs. X had a long-standing history of nausea and vomiting with temporary relief with chronic hot bathing but completely resolution with cessation of nabilone leading to the diagnosis of CHS.

Treatment

Nabilone was discontinued seven weeks after admission to the palliative care unit, nausea and vomiting resolved, but pain escalated. Attempt to reinitiate nabilone to help with the pain led to more severe episodes of nausea and vomiting. As CHS was suspected, she was switched to hydromorphone and gabapentin to control her pain. Serotonin and norepinephrine reuptake inhibitors were later added to augment analgesia.

Outcome and follow-up

Mrs. X's pain became well controlled with opioids, gabapentin, and selective serotonin reuptake inhibitors, and there has been no recurrence of nausea and vomiting since the cessation of nabilone. She died eventually in the palliative care unit while being comfortable with the support of palliative care team and her loved ones at bed side.

Discussion

Clinicians should be aware of the risk of CHS with chronic use of cannabis [6]. Best practice guidelines assert that hyperemesis management should include adequate hydration and administration of non-cannabinoid derived antiemetics as a first choice. In Mrs. X case nabilone led to the development of CHS, and as a result she was switched to opioids, gabapentin, and selective serotonin reuptake inhibitors to target her pain. Nausea and vomiting subsided and no additional intervention needed from this regard as time passed post chemotherapy. If she would become symptomatic from nausea and vomiting perspectives alternative antiemetics could be used as the drug of choice in this situation.

There is an association between CHS and long-term cannabis usage which completely ceased with cannabis discontinuation [7]. In the described case, discontinuation of nabilone led to the complete resolution of nausea and vomiting, and re-initiation of nabilone resulted in more severe nausea and vomiting. It solidifies that Mrs. X's nausea and vomiting was induced by cannabis. Prolonged nabilone use can result in an increased level of synthetic cannabinoids in the blood, causing CHS [8]. The dosage of cannabis used by patients leading to CHS are undetermined, but the duration of cannabis usage varies between 6 months to 11 years has been shown to produce hyperemesis [8-11]. In Mrs. X's case, nabilone was used for 5 years to manage pain, nausea and vomiting.

Management of CHS

Besides cannabinoids cessation [8], there are other solutions to manage nausea and vomiting in patients with CHS such as taking hot baths, which provides temporary relief only. Delta (9)-tetrahydrocannabinol in cannabinoids may disrupt thermoregulation, and a hot shower may attenuate its symptoms. Hot water may redirect blood to the skin and away from the guts, which can reduce nausea and vomiting. In Mrs. X's case, hot baths were used initially to alleviate nausea and vomiting which, provided a relief only for a few hours, but had a diagnostic value. The unique clinical sign of compulsive hot water bathing should be highlighted in patient history, as an important diagnostic marker [8]. Side effects of chronic hot water bathing are associated with weight loss, volume reduction and rupture of the esophagus [12].

Additionally, capsaicin cream has been used for induced cannabinoid hyperemesis relief and could be useful in patients like Mrs. X to achieve the same effects without the burden of constant bath taking [2,13]. In a randomized controlled trial, abdominal application of capsaicin has been shown to significantly reduce nausea and vomiting 60 min after administration [14]. Topical capsaicin has been shown to be cost-effective in emergency departments in managing CHS, as patients reported relief of nausea and vomiting and faster discharge [15,16].

First-generation of antipsychotics have also shown to be effective in managing CHS, including droperidol and haloperidol. Intravenous administration of droperidol significantly reduced nausea and vomiting, as well as length of stay in the emergency department for older adults [17]. Similarly, intravenous use of haloperidol has been effective in treating severe refractory CHS in the emergency

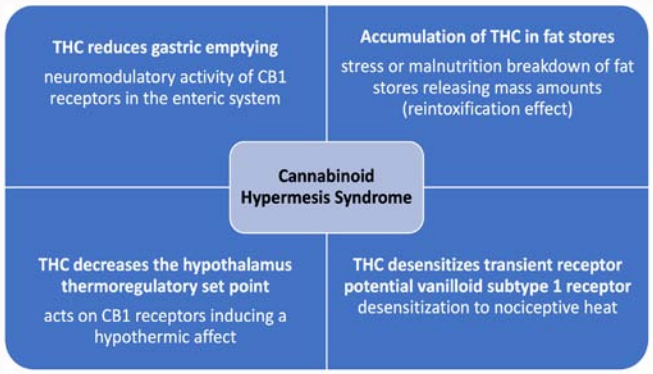

Figure 1: CHS Mechanisms.

department. For individuals unresponsive to antiemetics, haloperidol rapidly led to complete resolution of nausea and vomiting [18-20].

Proposed mechanisms of CHS

The most common chemical in cannabis, delta (9)-tetrahydrocannabinol, has neuromodulatory antiemetic effects on CB1 and CB2 cannabinoid receptors. Delta (9)-tetrahydrocannabinol activation of these receptors is known to reduce gastric emptying [21]. It is hypothesized there is gastrointestinal CB1 overriding, where delta (9)-tetrahydrocannabinol activation in the central nervous system is overridden by its effect on the enteric system, leading to CHS, which was probably observed in Mrs. X [21].

Accumulation of the lipid-soluble delta (9)-tetrahydrocannabinol in cerebral fat has also been known to cause nausea and vomiting [9]. During stress or food deprivation the body breaks down fat and a large reservoir of stored delta (9)-tetrahydrocannabinol is released causing a "reintoxification effect" [22]. The stress and food deprivation induced by malignancy and chemotherapy in Mrs. X's case could have contributed to the breakdown of fat causing nausea and vomiting. The proposed mechanisms for CHS can be found in Figure 1.

Drug-drug interactions and CHS

For patients with cancer, drug-drug interactions between chemotherapy agents may contribute to nausea and vomiting, which was possibly observed in Mrs. X's case. The interaction between nabilone and her other medications could lead to undesirable adverse events. Cisplatin and paclitaxel could increase the paclitaxel level by reducing drug clearance through the kidneys, resulting in delayed metabolism of nabilone and leading to toxicity, manifested by CHS [23].

It is important to keep in mind that combined use of lorazepam and nabilone could lead to increase sedation, hence this combination should be monitored closely. Further, benzodiazepines should be used with caution due to the potential risk of addiction, development of delirium and falls in older adults [24]. Haloperidol should be used with caution in patients with dementia and Parkinson's disease, as dopamine blockade can dramatically worsen symptoms leading to Tardive dyskinesia, cognitive decline and non-verbal fluency causing incapacitation [25]. Interestingly enough, haloperidol has been associated with increased agitation in patients with dementia despite being frequently used to control responsive behavior in this population [26]. In Mrs. X's case, typical treatment with haloperidol for controlling nausea and vomiting was unsuccessful and only resulted in short term benefit, and additionally was associated with drowsiness and agitation. Successful recognition and careful selection of pharmacological treatment for CHS is especially important in aged individuals with multiple co-morbidities like was seen in Mrs. X's case.

Management of CHS

Cannabinoid induced hyperemesis can be a life-threatening situation. A recent study by Soota et al. [27] described three fatal cases presumably caused by CHS. Thus, it is important to keep in mind that using cannabis for over 6 months, especially in aged individual with multiple comorbidities may lead to nausea and vomiting induced by cannabis toxicity [28], and urgent cannabis discontinuation should be considered. Medication interactions and polypharmacy in patients undergoing other treatments may impair renal function and results in drug toxicity manifested in described CHS [29].

Currently there are high levels of misdiagnosis of CHS as it can be masked by other conditions such as malignancy, chemotherapy, cyclic vomiting syndrome, eating disorders or drug-seeking behavior [30]. Healthcare professionals should be alarmed that patients using synthetic cannabinoids are more prone to the development of CHS compared to natural marijuana users [30].

Conclusion

With the worldwide growing usage of cannabis due to its legalization, cases of CHS are on the rise, and widespread awareness is vital for healthcare practitioners in order to recognize and appropriately manage nausea and vomiting induced by long-term cannabis intake, especially in palliative care settings while dealing with this frail population. Although, the findings in this case report cannot be generalized to the whole population timely recognition, diagnosis and management are imperative to mediate effects of cannabis toxicity. Further research is warranted to solidify the best management options of CHS.

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