

## **Cluster Attacks Responsive to Recreational Cannabis and Dronabinol**

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Pharmacological preparations of cannabinoid compounds have a variety of therapeutic uses in medicine, including different pain syndromes, but have not been previously reported as beneficial for cluster headache. We present a patient with cluster headache who was refractory to multiple acute and preventive medications but successfully aborted his attacks with recreational marijuana use; subsequent use of dronabinol provided equally effective pain relief. The beneficial effect may be related to the high concentration of cannabinoid receptors in the hypothalamus, which has been implicated as a site of dysfunction in neuroimaging studies of patients with cluster headache.

Key words: cluster headache, cannabis, dronabinol Abbreviations: DHE, dihydroergotamine

Cannabis preparations have often been used in the medical community to treat pain, nausea, and anorexia. We report a unique patient with cluster headache refractory to multiple acute and preventive medications whose attacks responded promptly to recreational marijuana use. The use of dronabinol, capsules of tetrahydrocannabinol in sesame oil, provided equally effective acute pain relief. 1

### **CASE REPORT**

A 19-year-old right-handed university student presented to the Montefiore Headache Center for evaluation and management of his cluster headaches. Over the past 2 years, he had a cyclical pattern of stereotyped attacks occurring predictably every 1 to 2 months, lasting approximately 2 weeks. During these 2-week cluster periods, he experienced 1 attack every other day. Each cluster period was typically followed by a remission phase lasting 1 to 2 months. However, over the past 3 months, the frequency gradually increased to 1 to 2 attacks daily. The majority of attacks would abruptly awaken him from sleep at 12:30 am or 4:30 am with excruciating right temporal and peri-orbital pain. Each episode lasted 3 to 4 h untreated, with the pain reaching maximal intensity within 10 min and declining within 10 min at its conclusion. Associated symptoms included ipsilateral tearing and ptosis as well as photophobia and phonophobia. With 60% of attacks, he experienced a visual aura of a colored zigzag arc in the superior hemifield of his vision in the 10 min before pain onset. During the attacks, he experienced restlessness, feeling the need to move about, or if driving a car he would accelerate to a faster speed. He did not drink alcohol, but noted that marijuana use at the onset of his headaches consistently brought complete relief within 5 min of inhalation for each attack. The patient's mother suffered from migraine and cluster headaches. General physical and neurological examinations were normal. Routine blood tests including serum prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), and total and free testosterone levels were normal; urine drug screen was positive for cannabinoids. Brain magnetic resonance imaging and computerized tomography angiography examinations were unremarkable. Transitional treatment with a tapering course of prednisone over 3 weeks and a greater occipital nerve block performed with 40 mg of methylprednisolone acetate in 1 mL and 3 mL of 0.5% bupivacaine were without benefit. Numerous prophylactic medications were tried in combination with either minimal success or intolerable adverse effects, including verapamil, lithium, sodium valproate, melatonin, topiramate, nifedipine, indomethacin, zonisamide, venlafaxine, ergotamine tartrate, and clonazepam. Because of its lack of availability in the United States and the patient's concern about potential adverse effects, methysergide was not tried for prevention. Treatment with sumatriptan tablets, zolmitriptan nasal spray, ergotamine/caffeine, oxycodone, aspirin/butalbital/caffeine, acetaminophen/dichlorphenazone/isometheptene, and indomethacin was ineffective. The patient refused to use subcutaneous sumatriptan because of a strong aversion to needles. Given the lack of

responsiveness to multiple agents, dronabinol 5 mg was substituted for marijuana for acute treatment of his cluster headaches; dronabinol consistently provided dramatic relief within 5 to 15 min of ingestion. The patient was hospitalized for intractable cluster headache, with complete resolution of his pain after several courses of intravenous dihydroergotamine (DHE), metoclopramide, and diphenhydramine. He was discharged with tapering doses of DHE nasal spray and a regimen of topiramate, sodium valproate, and melatonin for prophylaxis. Following discharge from the hospital, the patient's headaches became less intense and less frequent, with an attack occurring every other day. Acute attacks remained consistently responsive only to dronabinol 5 mg.

## DISCUSSION

Cannabis and cannabinoid compounds have been used to treat pain and possibly headache for centuries. <sup>2</sup> There are 2 types of cannabinoid receptors in humans (CB1 and CB2), and only CB1 is expressed in the central nervous system. <sup>3</sup> These receptors are located presynaptically, and are thought to modulate neurotransmitter release. CB1 receptors are widely but not universally distributed in the central nervous system, and are particularly concentrated in the hypothalamus. A recent study in mice found CB1 receptors in axons innervating the majority of hypothalamic nuclei, with the exception of the suprachiasmatic and lateral mammillary nuclei. <sup>4</sup> Neuroimaging studies of different modalities have consistently highlighted the ipsilateral posterior hypothalamus as a site of pathology and activation in patients with cluster headache. <sup>5</sup> Dronabinol, a synthetic delta-9-tetrahydrocannabinoid, is currently Food and Drug Administration approved for the treatment of nausea and appetite stimulation. <sup>1</sup>

Our patient's rapid improvement of pain within 15 min of use is faster than the reported onset of action of 30 to 60 min. <sup>6</sup> This early response could represent a placebo effect. However, the multitude of treatment-responsive attacks, as well as the failure of other acute therapies, are evidence against that phenomenon. Data on cannabis use among patients with cluster headache are limited. In a recent French study of 113 patients with chronic cluster headache, 29 patients (26%) were regular cannabis consumers. <sup>7</sup> However, no mention is made regarding the use of cannabis specifically for acute treatment of cluster attacks. It may be of future interest to ascertain if pain relief can be achieved when recreational marijuana or dronabinol are used in a cluster attack. We would not recommend routine use of recreational or pharmacological preparations of cannabis for treatment of cluster headaches because of the risk of long-term dependence and other potential adverse effects. However, if our observation can be expanded to other sufferers of this disorder, the use of pharmaceutical cannabinoid compounds could play a role in the treatment of cluster attacks refractory to conventional acute agents. In addition, this observation may provide further insights into the underlying pathophysiology of cluster headache, including modulation of neurotransmitter release in the hypothalamus of cluster sufferers.

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