Case Study: Management of Post-Parotidectomy Neuropathic Pain with Tetrahydrocannabinol:cannabidiol (Sativex)

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ABSTRACT

Effective treatment and management of neuropathic pain have been limited. Tetrahydrocannabinol:cannabidiol (THC:CBD) endocannabinoid buccomucosal spray (Sativex) is used in this case study to treat a patient suffering from neuropathic pain post-parotidectomy. Furthermore, this particular case study shows that cannabinoids may be effective, at least in part, through a central mechanism to relieve allodynia. This patient's allodynia was treated with Sativex buccomucosal spray. Six weeks later, the patient returned to the clinic with pain symptoms alleviated and transient decrease in alertness as the only side effect experienced. Two years since the initiation of Sativex treatment for allodynia, the patient has not experienced any relapse and is now working and fully functional. This case study demonstrates a successful off-label use of Sativex to treat post-parotidectomy neuropathic pain. Sativex is currently indicated in Canada to treat neuropathic pain only in multiple sclerosis and cancer. This is the first case study to report successful treatment of post-parotidectomy neuropathic pain with THC:CBD (Sativex) buccomucosal spray.

KEYWORDS: *Sativex, allodynia, neuropathic pain, tetrahydrocannabinol:cannabidiol*

INTRODUCTION

Chronic pain commonly causes disability and is a large expense in the health care budget.[1] There is strong evidence that the presence and severity of neuropathic pain in patients are associated with greater impairment in health-related quality of life.[1]

Moulin states that there are three classic symptoms of neuropathic pain, and for each patient, they are present to a variable degree.[2] The first symptom is allodynia, the unusual perception of pain to a stimulus that is usually innocuous. The second is the sensation that an area is "on fire", which is characteristic of a burning dysesthesia. The third is paroxysmal pain, which is commonly fleeting and intense.

The mechanism of persistent chronic central neuropathic pain – a condition in which pain continues to be reported by the patient in the absence of any obvious peripheral damage – is quite complex (Figure 1). This condition usually presents itself following excessive activation of peripheral nociceptors or after peripheral nerve damage has occurred.[2] There is evidence to support both functional and anatomical changes in the central nervous system (CNS) that might explain neuropathic pain.

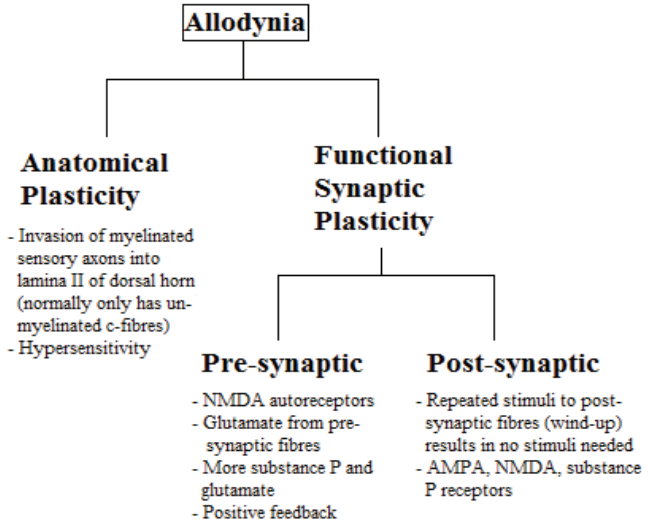

Figure 1. Mechanisms of Allodynia

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Functional Synaptic Plasticity

This is a mechanism that can be further specified into two categories: pre-synaptic and post-synaptic mechanisms. The pre-synaptic mechanism states that the pre-synaptic NMDA (n-methyl d-aspartic acid) receptors are acting as autoreceptors, stimulated by glutamate released by the pre-synaptic fibres. This would result in an increase release of substance P and glutamate, which would create a positive feedback cycle leading to hypersensitivity and allodynia.[3] The post-synaptic mechanism explains that the response to repeated stimuli by postsynaptic neurons increases over time (or 'wind-up') until there is spontaneous activity in the absence of any stimuli. This mechanism may involve AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA glutaminergic receptors as well as the activation of substance P receptors.[3] Furthermore, Martin *et al.*[4] report that the gamma isoform of protein kinase C is induced in lamina II in injuries that result in allodynia and hyperalgesia.

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Anatomical Plasticity

In the anatomical mechanism of allodynia and hyperalgesia, myelinated sensory axons sprout and invade lamina II of the dorsal horn. Normally, lamina II is the site of unmyelinated C-fibres that carry pain stimuli. Therefore, the invasion of myelinated sensory fibres into lamina II allows even non-noxious stimuli to activate the pain pathway.[3]

The options for first-line therapy of chronic neuropathic pain include antiepileptics, antidepressants, opioids, and topical local anesthetics.[5-9] However, these agents appear similar in analgesic efficacy and tolerability, despite their differences in mechanism of action.[5-9] Therefore, there is a need for better pain control than is currently available. Thus far, there has been substantial support for the administration of cannabinoids to treat chronic pain and its associated symptoms, such as disability, psychological distress, or sleep pattern changes.[2, 5-9,10-13]

Cannabinoids suppress neuropathic nociception in animal models of traumatic nerve injury through cannabinoid CB1 and CB2 receptor-specific mechanisms.[14] CB1 receptors are most prevalent in the CNS, and CB2 receptors are predominantly, but not exclusively, outside the CNS.[14] Interestingly, studies of a central mechanism of cannabinoid pain suppression show evidence of CB1 receptor afferents originating supraspinally and anti-allodynic effects being mediated at the level of the spinal cord.[13,14]

There are very few randomized controlled trials on the use of smoked cannabis. One trial using smoked cannabis to treat neuropathy in HIV patients showed a 30% pain reduction, in comparison to 15% in the placebo group.[15] However, in a study from Canada, patients with chronic pain treated with inhaled cannabis did not show changes in acute neuropathic pain scores.[16] Overall, it is unlikely that smoked cannabis will be approved by the Food and Drug Administration (FDA) because of a lack of Phase III clinical trials, inconsistent standardization of the drug, and health issues related to smoking. Nonetheless, government approved research programs using standardized herbal cannabis have been approved for chronic pain in Canada.[17]

Oral tetrahydrocannabinol (THC) (dronabinol) was approved in the United States for chemotherapy-associated nausea in 1985; however, it has mixed results with pain relief.[17] Nabilone (Cesamet), a synthetic analogue of THC with greater potency than natural THC, was developed to treat nausea and emesis from chemotherapy.[17] Prior case reports have shown nabilone to be effective for pain relief; however, sedation and dysphoria are prominent side effects.[18]

Tetrahydrocannabinol:cannabidiol (THC:CBD) (Sativex) is administered by spray and contains THC, CBD, minor cannabinoids, and terpenoids, as well as ethanol, propylene glycol excipients, and peppermint flavoring.[17] In Canada, Sativex is approved for multiple sclerosis-related pain and cancer pain but not for post-surgical neuropathic pain. Adverse effects of Sativex include complaints of oral stinging, bad taste, dry mouth, nausea, and dizziness.[17]

This article reviews a case study of a patient whose symptoms were successfully treated with a THC:CBD endocannabinoid system modulator (Sativex) buccomucosal spray after a 14-year history of post-surgical neuropathic pain, where other treatments were ineffective for pain control.

CASE REPORT

A 46-year-old Caucasian female presented to the St. Paul's Hospital Chronic Pain Program in Vancouver, Canada two weeks post-parotidectomy with hypersensitivity to clothing affecting her right neck and shoulder girdle radiating down to the inferomedial border of the scapula. This previously healthy librarian first presented with these specific symptoms 14 years ago when she had her right parotid gland resected due to a benign tumor. Post-surgically, Frey's syndrome was noted. Furthermore, this patient had right facial palsy and numbness in the distributions of the right V2 and V3 trigeminal nerve as well as sympathetic nervous system involvement. The patient slowly recovered from these post-surgical symptoms over a six-month period. However, the recovery was followed by an awareness of hyperesthesia to clothing involving the right trapezius and parascapular region. Interestingly, pain was specific to clothing and not to touch, temperature variations, or water during showering. Muscle spasms were also noted to develop at this time.

The muscle spasms associated with sensory allodynia were relieved by cyclobenzaprine (Flexeril), 30 mg at bedtime. Furthermore, gabapentin (Neurontin) at 900mg three times daily was partially beneficial in reducing hyperesthesia.

The patient was given multiple modalities of treatment over the past 14 years without significant benefit. Physical modalities such as massage have helped in the short term, but no long term improvements were observed. Acupuncture and moderate physical activity were not helpful. Pharmaceuticals were similarly ineffective. Trials of transcutaneous electrical nerve stimulation (TENS) and botulinum (Botox) injections were performed. Two hundred units of Botox were injected specifically into the trapezium region and then repeated three months later. Although both TENS and Botox relieved symptoms temporarily (three to six months), they lost their efficacy after several re-administrations.

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General examination revealed a pleasant lady in no acute distress and had a normal Beck Depression Score. She did not wear clothing above the T2 level due to the allodynia. There was a visible surgical scar from her right parotidectomy. Vitals were stable. Precordial examination was unremarkable. Neurological examinations revealed hypersensitivity to pin prick affecting the right V2 dermatome. There was no facial asymmetry. There were no sensory deficits in terms of allodynia to light touch, temperature, or mechanical pressure. Neurological exams were otherwise normal. Magnetic Resonance Imaging (MRI) and Ultrasound (US) of the right supraspinatus area and cervical spine as well as otolaryngological exam were unremarkable.

The patient was subsequently diagnosed with central neuropathic pain due to misrepresentation of the sensory pathway superimposed upon Frey’s syndrome following a right parotidectomy.

Low dose baclofen at 5-10mg twice a day was prescribed for muscle spasms. In addition, Sativex buccomucosal spray was used for pain. Six weeks later, the patient returned with all symptoms alleviated. The patient was using Sativex buccal spray three times per day. All other medications were discontinued. Three years later, treatment doses have not changed, and the patient is back at work and fully functional.

DISCUSSION

Sativex was one of the first cannabis-based medications to be approved as a prescription medication. It is derived from the extracts of the Cannibis sativa plant. The active cannabinoids, THC and CBD, are produced in high yields from this plant. Sativex has been proven to be more effective than placebo in alleviating central neuropathic pain.[7] This particular case study shows that the cannabinoids may be effective in treating post-parotidectomy neuropathic pain.

Barnes[12] describes Sativex as a treatment for both spasticity and neuropathic pain. The ability to treat both these symptoms proved to be “killing two birds with one stone” in our case study. In just five weeks, our patient returned to the St. Paul’s Chronic Pain Program Clinic with remarkable results. After 14 years, her symptoms had resolved with three sprays of Sativex per day: one spray in the morning at eight followed by a second spray at noon and then another at six in the evening. The only side effect noticed by the patient was temporary episodes of decreased alertness one hour after each spray, lasting for approximately 30 minutes. There has been no relapse of symptoms after three years, and she is very pleased with her response to the medication.

To our knowledge, this is the first case of post-parotidectomy neuropathic pain treated successfully with Sativex. In conclusion, Sativex may be an effective treatment for post-parotidectomy neuropathic pain refractory to other treatments.

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