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Case Report

Treatment using cannabidiol in a horse with mechanical allodynia

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Summary

A 4-year-old Quarter Horse mare was seen in the field by Colorado State University's Equine Sports Medicine Service for a 5-week history of marked sensitivity to touch near the withers/shoulder region. On examination, the mare showed a marked adverse response to light touch over the caudal neck and withers region. Diagnostic imaging of the caudal neck, withers and shoulder region showed no significant abnormalities. Vital parameters, complete blood count and chemistry profile were also within normal limits, as was a reproductive ultrasound examination. The mare received dexamethasone, gabapentin, magnesium/vitamin E, prednisolone and aquapuncture with no improvement in clinical signs. The mare was then started on pure crystalline cannabidiol (250 mg by mouth twice daily), which resolved the clinical signs after 2 days.

Introduction

Use of cannabidiol (CBD) has gained relatively recent popularity in human medicine for treatment of a variety of conditions, including epilepsy, Parkinson's and anxiety conditions (Zuardi *et al*. 2009; Chagas *et al*. 2014; Shannon and Opila-Lehman 2016; Tzadok *et al*. 2016). Cannabidiol is the major nonpsychoactive component of *Cannibus sativa* (Welty *et al*. 2014); therefore, administration does not result in any psychotic effects (Chagas *et al*. 2014). However, research studies show positive effects of CBD alone (without the psychoactive component, Δ^9-tetrahydrocannabinol [THC]), including antinociceptive and anti-inflammatory effects (Agarwal *et al*. 2007; Bushlin *et al*. 2010; Desroches *et al*. 2014; Shannon and Opila-Lehman 2016). A study evaluating the safety and efficacy of CBD in dogs with osteoarthritis showed positive pain-modulating effects (Gamble *et al*. 2018). While additional CBD studies using laboratory animals have been published, no equine studies have been reported.

Hyperaesthesia has been well reported in the cat, although the pathogenesis is still unknown. Cats with feline hyperaesthesia syndrome exhibit symptoms such as tail chasing, biting or licking the lumbar area, and muscle spasms, which may be elicited by light touch. Multiple treatments have been employed, including antiepileptic drugs, anti-inflammatories, adjuvant analgesics (gabapentin) and behaviour-modifying drugs (Amengual Batle *et al*. 2019). While this syndrome has not been described in the horse, cutaneous hypersensitivity can be seen in horses with insect hypersensitivities (Fadok and Greiner 1990; Schaffartzik *et al*. 2012). In humans, hypersensitivity to touch in cases of chronic myofascial trigger points has been reported, known as mechanical hyperalgesia (Meng *et al*. 2015). These conditions describe forms of allodynia, a painful response elicited from a nonpainful stimulus. Mechanical allodynia is specifically defined as a painful sensation caused by an innocuous stimulus such as light touch (Lolignier *et al*. 2015). This case describes the clinical findings of a horse with mechanical allodynia and successful treatment with CBD.

Case history

A 4-year-old Quarter Horse mare was seen in the field by Colorado State University's Equine Sports Medicine Service for a 5-week history of sensitivity to touch near the withers/shoulder region. At the onset of the clinical signs, the mare had been seen violently bucking and reacting to an unknown stimulus. At the time, it was presumed that she may have been stung by an insect. Shortly thereafter, she displayed a similar episode while being lunged while tacked. Following these episodes, the mare would twitch uncontrollably when anyone would touch the withers/shoulder region, often becoming dangerous in her stall. The mare was treated with two doses of dexamethasone (20 mg i.v. q. 24 h) and started on vitamin E (5000 IU daily per os) 2 weeks prior to the presentation, which mildly improved the clinical signs.

Clinical findings

The mare was in good body condition (body condition score 4/9) and was bright, alert and responsive. Heart rate, respiratory rate and rectal temperature were within normal limits. Initially, the mare behaved normally, allowing light palpation of the neck and withers on the left side. Touching near the withers on the right side resulted in a violent reaction consisting of twitching, kicking out behind and striking out in front. Subsequently, this could be reproduced by pointing in the general direction of the withers, without any direct contact. She would tolerate firm palpation of the ventral aspect of her neck and brushing/stroking of her neck but would no longer tolerate any touching of the top of her scapula/withers region. No abnormal soft tissue swellings or any other abnormalities could be appreciated on limited palpation. A dynamic examination did not reveal any overt lameness. Neurological exam included assessment of cranial nerves, static and dynamic tail pulls, small circles and walking with the head elevated. All of these findings were within normal limits. The mare was observed walking over the threshold of her stall multiple times without incident but the

facilities did not allow walking over a curb and/or up and down a hill. Lateral radiographs of the cervical spine and withers, including the cranial thoracic spine, were performed and revealed no abnormalities. Ultrasound of the caudal cervical, withers and shoulder region could not be performed safely in the field, even with sedation. Complete blood count and diagnostic profile showed no abnormalities.

Diagnosis

Differential diagnoses included syringohydromyelia, trauma or idiopathic neuropathic pain leading to cutaneous hyperaesthesia and mechanical allodynia, and/or a behavioural component.

Treatment

The mare was placed on a course of gabapentin (15 mg/kg per os t.i.d. for 5 weeks followed by a 2-week weaning period), which did not result in any improvement in clinical signs. Systemic treatment with prednisolone was then instituted (1 mg/kg per os q. 24 h for 2 weeks, followed by 0.5 mg/kg per os q. 24 h for an additional 2 weeks, and 0.5 mg/kg per os q. 48 h for 2 weeks). This treatment did not result in any improvement in clinical signs. Throughout, the mare continued to be fed a magnesium and vitamin E (5000 IU daily) supplement with no significant improvement.

Recheck examination was performed approximately 3 months after the initial assessment, with only mild improvement in clinical signs. The mare was moderate to markedly reactive to light touch over the neck, withers and back. She was most reactive near the withers, on the right side. The mare was more tolerant of firm pressure, with no significant trigger points appreciated over the thoracic or lumbar region when firm pressure was used. Reproductive ultrasound was performed, which showed moderate oedema in the uterine wall with several large follicles present on both ovaries, consistent with a normal heat cycle. A reproductive hormone panel was also performed, which revealed normal levels of progesterone, testosterone, inhibin B and anti-muellerian hormone. The mare was sedated with detomidine and butorphanol i.v., and aquapuncture with vitamin B12 was performed at acupuncture points around the withers/shoulder region, as well as at points influential for skin hypersensitivity. Options for further diagnostics, including referral for a neurological consultation and nuclear scintigraphy, were declined. Additional treatment options included placing the mare on Regumate (20 mL q. 24 h per os) to further rule out the reproductive tract as a cause of the mare's behaviour or reserpine (2.5 mg b.i.d. per os) to help rule out a purely behavioural cause. The owner elected instead to place the mare on CBD.

The mare was then placed on pure crystalline CBD at 250 mg by mouth twice daily. This formulation was fed on grain without any palatability issues.

Outcome

After 36 h on CBD, the mare exhibited significant improvement in clinical signs, including allowing both light and firm touch over the neck, withers and shoulder region. She was also able to be tacked for lungeing without any evidence of adverse behaviour. After approximately 60 days, the CBD dosage was decreased by half which resulted in recurrence of the clinical signs within 1 day. The initial dose of 250 mg twice daily was resumed and tapered more gradually over the next 2 months without any subsequent recurrences of clinical signs. The mare is currently maintained on 150 mg per os CBD once daily with the owner reporting a 90% improvement of clinical signs overall.

Discussion

This study describes a mare with apparent cutaneous hyperaesthesia and mechanical allodynia, predominantly around the withers/shoulder region. While the exact cause of onset of clinical signs is unknown, it was thought that an insect sting may have been the source. This may have resulted in local histamine release, creating local inflammation and stimulation of nociceptors. This may have then resulted in central sensitisation and neuropathic pain. Neuropathic pain can result in allodynia, hyperalgesia (exaggerated response to painful stimuli) and changes in motor control (Bushlin *et al*. 2010). However, if neuropathic pain was the predominant source of the clinical signs, at least some improvement could be expected with gabapentin treatment. While the dosing of gabapentin in clinical cases is highly variable, the authors have seen reasonable clinical response with the dosage used in the current case in horses with neuropathic pain. However, a higher dosage may have been effective in alleviating the mare's clinical signs and the lack of response does not rule out neuropathic pain in this case. In addition, insect hypersensitivities often respond positively to treatment with corticosteroids, which was not the case with this mare. A behavioural component to the mare's behaviour is also possible and may explain the lack of improvement with gabapentin and prednisolone.

Additional diagnostics that could be considered in this case included oblique radiographs of the cervical spine, cerebrospinal fluid (CSF) analysis and nuclear scintigraphy. At the author's institution, the standard protocol is to obtain oblique radiographs of the cervical spine only when an abnormality is detected on the lateral projections. In this case, the lateral projections were within normal limits so oblique projections were not pursued. However, due to the unusual nature of the case, oblique radiographic projections may have been warranted. Cerebrospinal fluid analysis would have provided additional information as to an infectious cause of the mare's clinical signs, such as equine protozoal myelitis and bacterial meningitis. However, given the lack of other neurological signs, safety concerns with performing this procedure in the field and owner preference, this diagnostic procedure was not pursued. A nuclear scintigraphic examination, to evaluate for potential sites of trauma, was offered but declined by the owner.

Syringohydromyelia is an uncommonly reported disorder in the horse. Syringohydromyelia is characterised by abnormal fluid-filled cavitary lesions within the spinal cord that can extend through one to several vertebral segments. This condition has been described in both foals (congenital) and adult horses (acquired). In adult horses, clinical signs can include self-mutilating behaviour focused on one area, indicating a regional allodynia, as well as sudden onset of fractious behaviour (Sponsellar *et al*. 2011; Kurz *et al*. 2018). Acquired forms of this disorder are thought to occur following

a traumatic episode (Sponsellar *et al*. 2011). All currently reported cases in the horse have been diagnosed based on post-mortem findings. In small animals and humans, a diagnosis can be made on MRI (Iskandar *et al*. 1998; Kyoshima *et al*. 2002) and contrast-enhanced computed tomography (CT) (MacKillop *et al*. 2006). In horses, MRI evaluation of the caudal cervical spine is not currently possible ante-mortem. However, contrast-enhanced CT of the caudal cervical region can be performed and would be a diagnostic option in this case.

Use of CBD resulted in resolution of the clinical signs after treatment for only 36 h. Cannabidiol has been shown to have improvement in nociception and neuropathic pain effects. Cannabidiol has been shown to act on G protein-coupled receptors, cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2), which are highly expressed in the hippocampus and other parts of the central nervous system (Welty *et al*. 2014). Mu receptors, a major opioid receptor, and CB1 have been shown to colocalise to the same neurons within the superficial dorsal horn of the spinal cord, the first site of synaptic contact for peripheral nociceptive afferents (Bushlin *et al*. 2010). Activation of opioid receptors with cannabinoids has also been suggested based on studies showing significant improvement in analgesia with use of a combination of cannabinoids and opioids, as compared to opioids alone (Bushlin *et al*. 2010; Maguire and France 2016, 2018).

Cannabinoid type 2 receptors are also located in the periphery in lymphoid tissue. CBD helps to mediate the release of cytokines from the immune cells in a manner that helps reduce inflammation and pain (Shannon and Opila-Lehman 2016). Cannabinoid type 1 receptors located in the brain also modulate neurotransmitter release that prevents excessive neuronal activity, resulting in a calming effect and reduced anxiety. The action on neurotransmitter release can also regulate movement, postural control and sensory perception. Because of these actions, CBD may have been effective in the current case by having an effect on pain, sensation and behaviour (anxiety associated with touch) (Shannon and Opila-Lehman 2016). Because CBD does not contain THC, psychotropic effects do not occur. This has been shown during use in both humans (Zuardi *et al*. 2009) and dogs (Gamble *et al*. 2018).

Three forms of cannabinoids have been described, including endogenous cannabinoids (endocannabinoids), herbal cannabinoids (phytocannabinoids) and synthetic cannabinoids. Multiple endocannabinoids exist and are formed from membrane phospholipids in response to increases in intracellular calcium. Within the nervous system, endocannabinoids are released from postsynaptic neurons to bind to presynaptic CB1 receptors, resulting in inhibition of GABA and glutamate release. Phytocannabinoids are produced by plants, particularly female *Cannabis sativa* plants, and are present within the resin of the herb. Synthetic cannabinoids are manufactured compounds that bind to cannabinoid receptors. Both phytocannabinoids and synthetic cannabinoids mimic the effects of endocannabinoids (Landa *et al*. 2016).

Limitations of the described case report include the lack of a complete set of diagnostic tests to rule out all neurological/traumatic causes of the clinical signs. While a more thorough evaluation of the case described would have been beneficial, in clinical practice it is unusual to be able to perform all diagnostic procedures. This case helps highlight the potential use of CBD for cases where traditional medications for pain/behaviour modification are needed and all diagnostic techniques cannot be performed. Description of additional cases would help further highlight the use of CBD for cases refractory to traditional medications/treatments. It is the hope of the authors that the description of this single case will help stimulate further research into the use of CBD in the horse.

The dose of CBD used in the horse in this report was based loosely on human dosing recommendations. The bioavailability of CBD has been shown to be 6% in humans with a half-life of 1–2 days when taken orally (Welty *et al*. 2014). The half-life in dogs has been shown to be 4.2 h at a dose of 2 mg/kg. Twice daily administration at this dose was effective at modulating pain associated with osteoarthritis (Gamble *et al*. 2018). The dosage used in the horse in this report was approximately 0.5 mg/kg twice daily and appeared to be effective even when the dose was gradually reduced to 0.33 mg/kg once daily. While CBD may be effective in the horse for pain and behaviour modulation, significant research is needed to establish the safety, bioavailability, dosage and drug interactions in equine cases.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

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Authorship

All authors were involved in the management of the case described, as well as the preparation and final approval of the manuscript.

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