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MEMANTINE IN NOCICEPTIVE PAIN MANAGEMENT: A CASE REPORT

Andrew Aboujaoude, BS[1], and Daltry Dott, MD[1,2]

Background: Memantine is a N-methyl-D-aspartate receptor antagonist that is prominently known as an Alzheimer's disease medication. In recent years, it has started to receive attention for pain management purposes, especially for neuropathic pain. There has been little focus on its use for nociceptive pain. We present a case where the use of memantine for nociceptive pain in a patient yielded significant associated improvement.

Case Report: A 49-year-old man presented with a one-year history of severe nociceptive left neck pain subsequent to a whiplash injury. The patient failed multiple first-line therapies and pursued consults with multiple specialties without symptomatic improvement. He was put on memantine with subsequent sustained resolution of his nociceptive neck pain.

Conclusions: Memantine's optimal safety profile and effectiveness in this case make it important that more human patient research be conducted to further explore its efficacy for nociceptive pain.

Key words: Nociceptive pain, memantine, inflammation, chronic pain, case report

BACKGROUND

Memantine is a drug that has been around for over a half century with its use having evolved to treat a variety of diseases. It was originally developed as a medication to treat diabetes with little success in the late 1960s (1). In the 1980s, it was discovered that this drug impacted central nervous system activity as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that was highly voltage-dependent (2), making the side effect of dizziness seen in other NMDA receptor antagonists less prominent (3). Due to its prevention of neuronal excitotoxicity along with its optimal side-effect profile, it became popularly used as a medication for moderate or severe Alzheimer's disease after multiple successful clinical trials in the early 2000s (4,5).

The fact that NMDA receptors are a central part of neuropathic pain pathways led to intrigue about the use of memantine for pain management purposes. A study by Carlton et al (6) was one of the first to demonstrate the potential utility of memantine for managing neuropathic pain when neuropathic monkeys showed decreased responses to cutaneous stimuli through spinal thalamic tract cells after memantine treatment. In humans, a 40-patient randomized clinical trial (7) demonstrated the utility of memantine vs placebo when it was shown to improve neuropathic pain for postmastectomy breast cancer patients. Nonetheless, the studies in humans for memantine management of neuropathic pain have been inconsistent. At times, memantine has been shown to demonstrate little to no improvement of neuropathic pain (8). Even more limiting is research related to memantine and nociception in both animal models and humans. From the limited animal models, Piovesan et al (9) demonstrated the efficacy of memantine in treating nociceptive pain in Norway rats. To this date, there has been little focus on studying the effects of memantine on nociceptive pain in humans. In this report, we demonstrate a case

From: [1]University of Texas Southwestern Medical Center, Dallas, TX; [2]University of Texas Southwestern Frisco Spine Clinic, Frisco, TX

Corresponding Author: Andrew Aboujaoude, BS, E-mail: andrew.aboujaoude@utsouthwestern.edu
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where the NMDA receptor antagonist memantine was used to treat a nociceptive pain patient with significant associated improvement.

CASE

A 49-year-old man presented to the pain medicine clinic with a one-year history of left neck pain that radiated to the left trapezius and posterior occipital region. The patient stated that he first developed this pain after experiencing a whiplash injury from being punched to the face during boxing training at the gym. He reported that it worsened in intensity in the past few months and rated it as an 8-9/10 in severity. He described it as a constant aching, burning, and sharp pain that was worse with flexion and leftward rotation of the neck. He stated that a massage helped alleviate the pain temporarily, but Tylenol and spinal decompression had no effect. The patient denied any associated numbness, tingling, weakness, or bowel and bladder incontinence. He reported a past medical history of hypertension, type 2 diabetes mellitus, and minor chronic bilateral hand neuropathy. His medications were amlodipine 5 mg qd, carvedilol 40 mg qd, olmesartan 40 mg qd, and insulin. The patient denied any past surgical history or family history pertinent to the case. He denied any history of smoking or recreational drug use, but drank 3 glasses of wine per week and was married.

On physical examination, the patient was in no acute distress and was alert and oriented to person, place, and time. He had a normal mood with a congruent affect. He demonstrated tenderness on palpation of the left trapezius. He had positive cervical facet loading bilaterally, but negative Hoffman's sign and Spurling's maneuver bilaterally. Neurological exam demonstrated grossly intact cranial nerves II-XII and 2+ bilateral biceps, triceps, and brachioradialis reflexes. He demonstrated 5/5 strength of bilateral upper extremities. A left cervicothoracic trigger point injections (TPIs) procedure was subsequently performed on the left trapezius, splenius cervicis, and levator scapulae using 4 mL of bupivacaine 0.25% without complications and providing 75% improvement in pain relief for approximately 6 hours. In addition, duloxetine 20 mg qd was started.

The patient stopped duloxetine 20 mg qd a few days later as it was not improving his pain and was causing drowsiness. He instead opted to start gabapentin 300 mg tid. One month later, he came in for follow-up reporting that the gabapentin did not improve his symptoms and also made him very drowsy, leading to its discontinuation. His cervical spine X-ray showed minimal cervical spondylosis, and cervical spine magnetic resonance imaging showed edema of the central and left aspect of the dens and anterior arch of C1 with minimal fluid within the anterior atlanto-dental interval. His cervical spine computed tomography showed severe post-traumatic arthritis of the left C1-C2 joint (Fig. 1). He was started on Robaxin 500 mg tid prn for his neck pain and muscle spasms with no improvement. He also started meloxicam and etodolac (300 mg TID prn) subsequent to a rheumatology referral with no improvements and no diagnosis of reactive arthritis. He received a surgical referral where he declined all surgical options. He underwent another left cervicothoracic TPIs procedure with significant improvement lasting for a month. Subsequently, he resumed having pain that was 5/10 in severity and underwent an additional TPIs procedure. He was also started on memantine 10 mg bid. After a month of this treatment, the patient reported a significant improvement in his neck pain with severity decreasing to 2/10 and no more disruption to function. Additionally, a physical exam demonstrated negative cervical facet loading bilaterally and no tenderness on palpation of the left trapezius. The patient has remained without pain complaints for 3 months since he started the memantine therapy.

DISCUSSION

This case report depicts a middle-age man with a one-year long history of nociceptive pain of the left neck that was successfully treated with memantine. Chronic nociceptive pain is characterized by damage to nonneural tissue leading to activation and oversensitization of the nociceptors in the setting of inflammatory cytokines. Although his pain was inflammatory in nature, medications effective for nociceptive pain (e.g., nonsteroidal anti-inflammatory drugs, duloxetine, etc) (10) failed to adequately manage it in his situation. This case illustrates the resolution of nociceptive pain with memantine, an NMDA receptor antagonist, whose impact on nociceptive pain has not been fully elucidated with research largely limited to a select number of animal models.

NMDA receptors are ligand-gated and voltage-gated channels that bind glutamate and glycine and open when both ligands are bound and the neuron is sufficiently depolarized. Even when the ligand is bound, preceding depolarization is also required to open the channel because it removes the magnesium ion blocker

in the channel that prevents the inward flow of calcium ions (11). Noxious stimuli induce the excessive release of glutamate from nociceptors when nonneural tissue is damaged (nociceptive pain) and from the neuron when it is directly damaged (neuropathic pain). This excessive glutamate over-activates NMDA receptors and leads to the pain sensation (12). The NMDA receptor antagonist memantine imitates the magnesium ion blocker only under the condition of prolonged NMDA receptor activation, making it a selective inhibitor for the inappropriate activation of the NMDA receptor. This is the classically proposed pathway in which memantine is suggested to suppress pain, especially with regard to the neuropathic pathway (13).

Memantine can be hypothesized to play a role in specifically suppressing the nociceptive pathway through multiple ways. The first way is by inhibiting the NMDA receptors of the thalamic ventroposterolateral nucleus neurons or second-order neurons that are over-activated as a result of the initial event of the excess glutamate released from the nociceptors (14). Another possible mechanism is through its suppression of oxidative stress via its actions of inhibiting the production of inflammatory factors (15). The final mechanism is through the direct inhibition of the nociceptors (16). In all situations, memantine inhibition of NMDA receptors only occurs when these receptors are over-activated, as most commonly seen in a pathological pain state (13).

Memantine has not received US Food and Drug Administration approval for chronic pain management (11). Nonetheless, it can be indicated when first-line treatments for chronic neuropathic pain have failed. In particular, it can be indicated as a treatment for fibromyalgia, phantom limb pain, complex regional pain syndrome, and postmastectomy pain (13). With regard to nociceptive pain, memantine is not currently indicated as a first-line therapy as there is very limited research on its efficacy.

However, given its safe profile, it can still be used for nociceptive pain when other drugs are not effective (12). In our situation, memantine was used to successfully treat chronic nociceptive pain after multiple previously failed drug treatments. The efficacy of memantine for nociceptive pain management in this patient makes it important to conduct more human patient research to better determine the efficacy of memantine for similar patients.

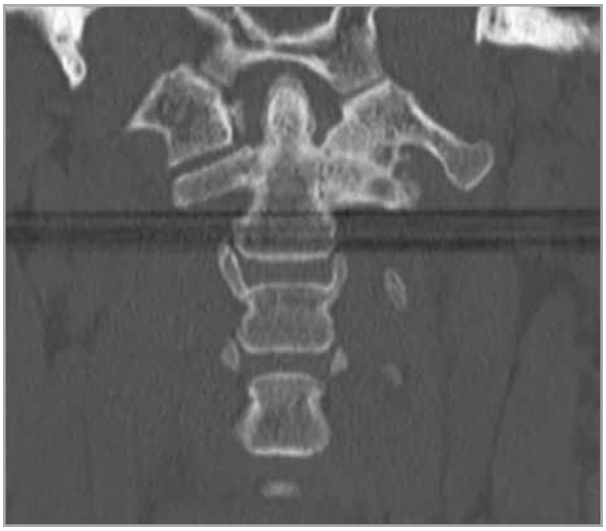

Fig. 1. CT cervical spine, coronal view, demonstrating C1-2 arthropathy

CONCLUSIONS

Chronic pain can be classified as neuropathic or nociceptive. The literature regarding memantine efficacy for neuropathic pain has been mixed, while the research has been very limited for nociceptive pain. Nonetheless, the promise of memantine in pain management is based on its potential ability to inhibit the effects of NMDA receptors that are over-activated in pathological pain states. In this case report of a middle-age man with chronic nociceptive left neck pain, memantine adequately improved his pain in the setting of multiple previously failed drug treatments. This case shows the potentially promising effects of memantine for nociceptive pain management with more extensive future research of larger sample size and longer patient follow-up being necessary to better determine the efficacy of memantine for patients with chronic nociceptive pain.

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