Successful Treatment of Neuropathic Pain and Mood Symptoms with Duloxetine in a Patient with West Nile Virus Infection

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Abstract: Neuropathic pain and concomitant mood disorder in West Nile Virus (WNV) infection seem difficult to control. A 57years old female diagnosed with neuroinvasive WNV infection presented with burning pain in the hands and feet consistent with neuropathic pain. In addition, a Patient Health Questionnaire-2 (PHQ-2) depression screening questionnaire administered to her was positive and on further interview she met diagnostic criteria for a mood disorder due to a general medical condition. Her symptoms included a loss of pleasure in all activities and mood lability. During her course of treatment, she also underwent five months of intensive physical therapy for rehabilitation and received intravenous immunoglobulin infusions for flaccid paralysis secondary to an inflammatory peripheral neuropathy attributed to WNV infection. The neuropathic pain and mood disorder dramatically disappeared after using duloxetine. Duloxetine is recommended for neuropathic pain management especially in patients with WNV infection.

Keywords: Neuropathic pain, virus infection.

1. INTRODUCTION

Neuroinvasive West Nile Virus (WNV) infection is a well-recognized clinical presentation of WNV infection and has been described as having broad effects on the central and peripheral nervous systems [1,2]. Duloxetine, a medication purposed for treating depression and painful diabetic peripheral neuropathy, dramatically relieved neuropathic pain and mood disorder in a female patient with WNV infection.

2. CASE DESCRIPTION

A 57 year old, 78 kg, previously healthy female presented to a primary care clinic with a three day history of generalized body aches, dizziness, fevers, chills, nausea, right leg weakness, visual hallucinations and severe pain in her hands and feet which she subjectively rated at a 10/10 on the visual analog scale. At the time of presentation, serum studies for WNV IgG and IgM were drawn, and six days later resulted as positive and indicative of acute infection. The patient was admitted as an inpatient on presentation for further workup and pain control, which consisted of intravenous (IV) and transdermal opioid therapy. However, this regimen was not effective in decreasing her pain below 7/10. Following her discharge from the hospital, she was evaluated in primary care and noted to have continued severe burning pain in her hands and feet despite treatment with transdermal fentanyl and oral ibuprofen. Further history elucidated mood symptoms including hopelessness, mood ability, and decreased appetite. Due to her disabling pain, she required an at-home caregiver to perform activities of daily living. On day 21 following initial presentation, she continued to report mood symptoms and severe pain and her pain management regimen at that time was modified to include the addition of duloxetine 30 mg by mouth once per day. Previous studies assessing the efficacy of duloxetine for the treatment of chemotherapy-induced painful peripheral neuropathy used dosages of 60 mg daily [3]. However, a lower initial dose of 30 mg daily was prescribed in this patient in order to reduce the risk for development of adverse effects.

On follow up examination seven days after initiation of duloxetine treatment, the patient reported significant improvement in her pain which she subjectively rated at a 5/10 as well as significant improvement in her mood symptoms, including increased appetite, less mood lability, and new optimism about the future. As a result, the patient was able to begin a comprehensive outpatient physical therapy and rehabilitation program. By day 14 following initiation of duloxetine treatment, the patient rated her pain at a 0/10 and reported significant improvement in mood symptoms. Furthermore, by day 14 of duloxetine treatment, she was able to independently perform activities of daily living. She reported minimal side effects during treatment with duloxetine. In addition, a complete blood count and comprehensive metabolic panel on day 17 of treatment with duloxetine demonstrated normal

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E-ISSN: 2310-9394/15 © 2015 Pharma Publisher

hemoglobin and hematocrit, normal creatinine, and normal transaminase levels.

The patient consistently reported complete pain relief. Her outpatient pain regimen of an oral NSAID (which was switched from ibuprofen to celecoxib due to gastrointestinal upset), transdermal fentanyl, and oral duloxetine was continued until day 55, at which time the oral NSAID and transdermal fentanyl were discontinued. She continued to take oral duloxetine at a dose of 30 mg per day throughout the full course of rehabilitation.

With regard to disease progression, following her initial inpatient hospitalization, the patient had persistent neurologic deficits consisting of an abnormal gait and balance, decreased monofilament sensation on bilateral plantar surfaces of feet and bilateral palmar surfaces of hands, hyporeflexia in the right patellar tendon, impaired vibration and temperature sensation in the right leg, and decreased motor strength of hip flexion and of the right leg. Therefore, an MRI of her brain was obtained on day 38 following presentation and demonstrated multiple deep white matter lesions and a transverse midline pontine lesion felt to be representative of encephalitis. She underwent further evaluation by a neurologist on day 48 following presentation including electromyelography (EMG) and nerve conduction studies (NCS). EMG and NCS demonstrated absent right sural sensory response, abnormal right peroneal F-wave response, prolongation of the right tibial motor nerve distal latency, abnormal right tibial F-wave response, and mild denervation of the right lower extremity distal muscles. In addition a lumbar puncture at this time demonstrated increased levels of IgG, increased protein, and positive titers for West Nile Virus IgG and IgM. These findings were supportive of a diagnosis of inflammatory peripheral neuropathy secondary to neuroinvasive WNV infection. Beginning on day 60 following initial presentation, the patient underwent a series of outpatient infusions of intravenous immunoglobulin (IVIG) therapy for her persistent neurologic deficits, which fully resolved by the end of the treatment. Her pain remained fully controlled with oral duloxetine at 30mg per day as the only pain medication from day 55 throughout her full course of rehabilitation.

Following initial workup and stabilization locally, the patient was transferred to a larger military treatment facility for comprehensive rehabilitation. She has made a full recovery from her illness and has no current physical limitations or persistent neurologic deficits.

3. DISCUSSION

Duloxetine dramatically relieved neuropathic pain and mood disorder in a female patient with WNV infection. Duloxetine is recommended for neuropathic pain management especially in WNV infection.

WNV is a member of the Flaviviridiae family, which also includes Japanese encephalitis, St. Louis encephalitis and Kunjin viruses. Symptoms of infection with WNV fall into a spectrum of severity, from an asymptomatic infection to a severe and debilitating neuroinvasive illness. While only one in every 150 individuals infected present with neuroinvasive infection, the symptoms and presentation can be dramatic and include encephalitis, meningitis, ataxia, cranial nerve palsies, polyradiculitis and acute flaccid paralysis similar to Guillian-Barre Syndrome [2,4]. A true poliomyelitis has also been described and supported by histologic demonstration of destruction to anterior horn cells [5-8].

Furthermore, a wide range of neurologic manifestations of WNV infection have been reported and include multifocal neuropathy [4] and peripheral neuropathy [1] and studies investigating viral infection in human brain cells suggest that cell damage is inflammatory in nature [9,10]. *In vitro* studies have demonstrated that release of pro-inflammatory cytokines and chemokines in response to microglial cell infection with the virus facilitate recruitment of virus-specific T cells into the CNS [9,10]. Death of WNV-infected cells occurs by either apoptosis or necrosis; however, spinal cord neurons in WNV-infected mice underwent apoptosis, suggesting a prominent inflammatory response to infection [10].

Inflammatory neuropathic pain is a product of the response to numerous factors including the release of immune mediators such as tumor necrosis factor alpha, interleukin 1, interleukin 6, nitric oxide, and prostaglandin. The analgesic effect on peripheral nociceptors secondary to this inflammatory cascade is either through direct action upon nociceptors or through indirect production of other mediators such as prost-aglandin, thromboxane, and prostacyclin [11]. From a pain perspective, this complex biochemical process affects both the peripheral and central nervous sys-tems, posing a challenge to achieve successful phar-macologic treatment of inflammatory neuropathic pain.

Emerging awareness of the cognitive and behavioral effects associated with neuroinvasive WNV infection have led to a multimodal approach to the

treatment of pain associated with the acute and chronic phases of the illness [14, 15]. In an epidemiologic study of the patients who contracted WNV in the initial 1999 US outbreak in New York City, 38% of patients subjectively reported symptoms of depression [16]. This association has also been observed in patients following other infectious neuroinvasive diseases such as Lyme disease, Nipah virus, and Saint Louis encephalitis [16]. Inflammation in the CNS, such as that which occurs upon infection with WNV can lead to alteration in levels of the neurotransmitter serotonin (5-HT), which may be contributory to the association of depression and neuroinvasive inflammatory disease [17].

Emerging recognition of the roles of 5-HT and norepinephrine (NE) as modulators of the descending inhibitory pain pathways in the central nervous system has led to recognition that treatment of pain with a dual 5-HT and NE reuptake inhibitor is beneficial for management of neuropathic pain symptoms. These dual reuptake inhibitors target both the 5-HT and noradrenergic receptor sites to increase the availability of the neurotransmitters 5-HT and NE, respectively, in the synaptic cleft. Furthermore, successful treatment of depressive symptoms through the modulation of 5-HT reuptake can lead to improved quality of life for patients with peripheral neuropathic pain [13]. Duloxetine, a reuptake inhibitor for both 5-HT and NE is FDA-approved for treatment of both depression and neuropathic pain [16].

Duloxetine was initially approved for treating depression and diabetic neuropathy. The mechanism of duloxetine for treating mood symptoms through 5-HT and NE reuptake is fairly well understood; however, the mechanism of its analgesic effect is less clear. 5-HT and NE have been implicated in the mediation of endogenous pain mechanisms *via* the descending inhibitory pain pathways and the potentiation of 5-HT and NE activity in the central nervous system is believed to be involved in duloxetine's pain inhibitory activity [18].

Duloxetine's analgesic action may also be related to its ability to block sodium channels in peripheral nociceptors. A recent study by Wang, *et al.* demonstrated that duloxetine preferentially blocks late Na^+ currents at the Nav1.7 Na^+ channel, which is also blocked by local anesthetics and tricyclic antidepressants [19]. Furthermore, the Nav1.7 Na^+ has been described as a molecular gatekeeper of pain, thus partially explaining the analgesic mechanism of action of duloxetine in this patient.

This case report demonstrates the successful treatment of neuroinvasive WNV associated with opioid-refractory, severe neuropathic pain symptoms and severe mood symptoms with duloxetine. To our knowledge, this is the first reported case in the literature describing the successful use of duloxetine in the setting of neuroinvasive WNV infection. In light of this successful case, further studies of duloxetine in the setting of CNS-inflammation associated neuropathic pain and mood symptoms should be pursued. Given the recent emergence of WNV as a major public health threat worldwide, additional treatment options to alleviate the debilitating symptoms associated with this infection are necessary.

DISCLOSURE

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

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Received on 19-05-2015 Accepted on 10-06-2015 Published on 31-12-2015

DOI: http://dx.doi.org/10.14205/2310-9394.2015.03.02.5

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