Profound Pain Reduction After Induction of Memantine Treatment in Two Patients with Severe Phantom Limb Pain

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Case Report

Profound Pain Reduction After Induction of Memantine Treatment in Two Patients with Severe Phantom Limb Pain

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We present the cases of two patients who suffered severe lower extremity injuries and subsequently developed phantom limb pain (PLP) that was refractory to high dose opioids and adjunctive pain medications. Both patients were receiving large doses of oral methadone, IV hydromorphone via a patient-controlled analgesia delivery system, and adjunctive medications including tricyclic antidepressants, nonsteroidal anti-inflammatory medications, and anti-epileptics. Despite these treatments, the patients had severe PLP. Upon induction of the oral *N*-methyl-D-aspartate receptor antagonist memantine, both patients had a profound reduction in their PLP without any apparent side effects from the medication.

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P hantom limb pain (PLP) is very common after limb amputation and has a reported incidence of up to 87% of amputees.[1] This type of pain can be difficult to treat and usually responds poorly to conventional pain treatments.[2–4] We report two cases of profound pain relief in amputees after induction of oral memantine. In one of the cases, the patient was rapidly titrated off a high dose of IV hydromorphone after beginning memantine and required treatment of opioid withdrawal symptoms. Both patients had almost complete resolution of pain shortly after beginning memantine.

CASE DESCRIPTION

Case 1

A 27-yr-old man, active duty in the United States Air Force, sustained severe traumatic injuries to the lower extremities from an aviation accident. He underwent bilateral through the knee amputations at an outside institution. When he came to our institution, approximately 1 mo after the amputation surgery, he was experiencing severe, uncontrollable PLP and stump pain. His medications at the time of arrival included oral methadone 10 mg TID, gabapentin

1200 mg TID, amitriptyline 75 mg QHS, and celecoxib 200 mg BID. A hydromorphone patient-controlled analgesia (PCA) was initiated and nearly 100 mg of IV hydromorphone was used every 24 h by the patient in addition to frequent large doses of IV fentanyl for breakthrough pain. Despite these efforts, the patient continued to have significant pain. Memantine was then initiated and quickly titrated to a dose of 10 mg BID. Approximately 24 h after beginning the memantine, the patient's hydromorphone use decreased by over half to 45 mg. The next day, the patient no longer required opioid therapy and denied any pain. He then developed complaints of diaphoresis, nausea, chills, abdominal pain, and exhibited tachycardia, mydriasis, and piloerection. After life-threatening conditions were excluded, the patient was given fentanyl 100 mcg IV and showed immediate improvement in his symptoms. Because of this response to fentanyl, in conjunction with the rapid decrease in hydromorphone usage over 2 days, the patient's symptoms and signs were attributed to opioid withdrawal. Transdermal clonidine and β-blocker therapy were initiated and provided relief of withdrawal symptoms.

We have continued to follow this patient every 2 to 4 wk in our chronic pain clinic for an 11 mo period after his initial injury. During the first 6 mo, we continued memantine 10 mg BID, gabapentin 1200 mg TID, amitriptyline 75 mg QHS, and celecoxib 200 mg BID, while titrating the patient off methadone from an initial dose of 10 mg TID. Several weeks after discontinuing methadone, he was taken off memantine; both gabapentin and amitriptyline were titrated down and discontinued 2 mo after stopping memantine. The patient remains on celecoxib and has continued aggressive physical and occupational therapy during his entire follow-up course and has had no complaints of pain.

Case 2

A 21-yr-old man, active duty in the United States Marine Corps, sustained a severe right lower extremity injury from an improvised explosive device and arrived to our institution approximately 1 wk after the initial injury. After attempts at limb salvage, the patient underwent a right below

the knee amputation a few days after arrival. One week after limb amputation, the patient developed PLP and underwent placement of multiple peripheral nerve block catheters and epidurals in addition to a hydromorphone PCA and IV fentanyl for pain control. He was also started on Nortriptyline and Gabapentin and titrated up to doses of 100 mg QHS and 600 mg TID, respectively. Over a 1 ½ mo course, the patient remained hospitalized because of continued PLP and additional surgical procedures. By hospital day 50, he was using 80 mg of IV hydromorphone per day in addition to oral methadone 5 mg TID with continued significant PLP. He was switched from Nortriptyline to Amitriptyline 50 mg QHS, further titrated upward on Gabapentin to 900 mg TID, and started on both transdermal clonidine 0.1 mg/day applied weekly and memantine. Over a 6 day period, the memantine was titrated upward to 15 mg TID, whereas the hydromorphone PCA and IV fentanyl were completely titrated off without any symptoms of withdrawal.

We continued to follow this patient in our chronic pain clinic for 6 mo after his initial injury. He was continued on memantine 10 mg BID (dose was reduced from 15 mg BID because of sedation), gabapentin 900 mg TID, amitriptyline 50 mg QHS, and transdermal clonidine 0.1 mg/day applied weekly and was titrated off methadone from an initial dose of 5 mg TID over 2 mo. After discontinuing methadone, he was titrated off all adjunct pain medications over 4 mo. He is currently taking no medications and continues to undergo physical and occupational therapy without significant complaints of pain.

DISCUSSION

PLP is a challenging entity to treat, partly because of its underlying pathophysiology.[5,6] It would appear that both functional and structural changes happen both centrally (above and below the brainstem) and peripherally that help maintain a state of chronic neuropathic pain, of which PLP is a subset.[7,8] N-methyl-ᴅ-aspartate (NMDA) receptors are thought to play an essential role in both central and peripheral sensitization processes. This probably results from excessive glutamate release or excessive glutamate receptor activation at the time of injury and continued release as the patient continues to experience pain.[9,10] Because of this, many investigators have investigated the NMDA receptor antagonists, such as memantine, to help modulate some of the receptor changes after amputation or pain-generating insults.

Memantine was first synthesized in the 1960s and underwent several clinical trials in Germany during the late 1980s for the treatment of dementia; however, after receiving Food and Drug Administration approval in 2003 for the treatment of Alzheimer 's disease, it has been widely prescribed for treatment of dementia, but its use in the treatment of chronic pain is relatively new.[9–11] Memantine's principal mechanism of action is blockade of current flow through the NMDA receptor channel.[12] It differs from first-generation NMDA receptor antagonists (i.e., ketamine) in that it demonstrates better patient tolerability and generates minimal hallucinogenic side effects.[11] Although both memantine and ketamine bind preferentially to open NMDA channels, have similar blocking and unblocking kinetics, and demonstrate a similar

voltage-dependent antagonism of the NMDA receptor, several differences may explain why these two drugs differ markedly in their clinical side effects.[12] First, the elimination half-life of oral memantine is 60–80 h compared to a half-life of 2.5 h for oral or IV ketamine; the faster pharmacokinetics of ketamine may lead to a spike in serum concentration of the drug, which results in significant psychomimetic effects.[12] Second, unlike ketamine, memantine's blockade of NMDA channels increases with rising concentrations of the agonists glutamate and glycine. This phenomenon of "sequential blocking" means that high agonist concentrations in the presence of memantine allow for blockade of nearly all NMDA receptors, whereas low agonist concentrations in the presence of memantine allow the NMDA receptors to support some synaptic inputs, possibly resulting in fewer psychomimetic effects.[12] Finally, memantine has the ability to bind at both a shallow and deep site within the NMDA receptor, whereas ketamine only binds to the deep site, a variation in binding sites which may cause a difference in inhibitory effects between the two drugs.[12]

Excessive NMDA receptor activation can lead not only to sensitization, but also to neuronal cell death secondary to the excessive influx of calcium through the receptor's associated ion channel. Because of NMDA receptor's role in the pathophysiology of many chronic conditions, including chronic pain and PLP, receptor antagonists have been used in an attempt to prevent or treat some of these conditions.[9,10] The problem of over-antagonism arises, however, because the same processes that lead to very high levels of calcium influx are, at lower levels, absolutely necessary for normal neuronal function. Because of over-antagonism, many of the drugs that have been tried have either been unsuccessful, or have had untoward or unacceptable side effects. Memantine is unique in that it preferentially blocks excessive NMDA receptor activity without disrupting normal activity.[9] It is an open channel blocker, meaning that it enters the ion channel preferentially when it is excessively open. Also, it dissociates with the receptor at a relatively fast rate, and thus does not appear to accumulate in the channel and interfere with normal activity. Because of these reasons, it seems that memantine could potentially be used as a successful treatment for neurological conditions that are mediated by overactive NMDA receptor activity, like persistent pain.

There have been mixed results in studies using memantine to treat chronic pain. In two double-blind, randomized trials, memantine was unsuccessful at showing a benefit in already- established chronic PLP.[7,13–15] However, other studies have shown that memantine had a significant pain reduction effect in a certain subset of amputees.[2,16] The success in this certain subset may derive from the fact that the

amputation and PLP had an early onset and memantine treatment was initiated in the early stages. However, a more recent case series of six patients showed that patients suffering from Complex Regional Pain Syndrome type II had significant reductions in pain after starting memantine. A revealing component of this case series was the improvement in functional magnetic resonance imaging after treatment.[17]

In summary, we report two cases in which the addition of memantine appeared to have a temporal correlation with significant pain reduction in patients with chronic PLP receiving high dose opioids. Although memantine has been reported to be ineffective in the treatment of chronic PLP in several double-blind and randomized trials, it seems that this drug may show some promise in the treatment of certain patients with this pain syndrome, as described in our case report.

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