Low Dose Naltrexone as Part of Multimodal Management of Pain in a Sickle Cell Patient: A Case Study

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Background

Sickle cell disease (SCD) affects 1 in 400 African Americans, making it the most common genetic disorder in that population. Sickling of red blood cells leads to vasoocclusive events that cause ischemia-induced inflammation and pain. Some patients have even described this pain as more severe than post-operative pain. These microvascular occlusions also cause an increase in release of chemokines and make patients more susceptible to infection and respiratory dysfunction. Due to their transient nature, acute exacerbations of pain during sickle cell crises are very challenging to manage. Psychosocial issues further complicate optimal analgesia and must also be managed, ideally in a multimodal, multi-disciplinary fashion.

Opioid analgesics, particularly morphine, are typically used as first-line agents in patients with acute pain crises in SCD. However, adequate analgesia in SCD with opioids is complicated by tolerance, dependence, sedation, gastrointestinal complications, respiratory depression, and pruritis. Emerging evidence also points towards poor efficacy with standard regimens. Traditional opioids have been shown to induce Toll-like receptor 4 (TLR4) signaling, leading opioid-induced proinflammatory cascades and potentially exacerbating neuropathic pain. Additionally, due to concern for potential addiction and stigma surrounding SCD patients, many patients are under-treated. New pharmacotherapies that provide appropriate pain relief while minimizing side effects and ameliorating concern for abuse potential provide a promising avenue for treatment in SCD.

Naltrexone is a mu-opioid and kappa-opioid receptor reversible competitive antagonist which is FDA-approved for opioid and alcohol dependence at standard doses of 50mg to 150mg. It has also been shown to increase opioid sensitivity and reduce opioid receptor density in rats, leading to enhanced endogenous and opioid analgesia (a phenomenon known as opioid rebound effect). While mu-opioid antagonism is the primary function of naltrexone, when used in doses of 1mg to 5mg, naltrexone inhibits microglial activation. In rat and in vitro models, naltrexone can inhibit TLR4 signaling, limiting or reversing the proinflammatory pathway that is upregulated by opiates.

Low-dose naltrexone has been used off-label for treatment of multiple sclerosis, Crohn's disease, and fibromyalgia to address pain and inflammation. Treatment of these conditions is also characterized by utilization of a multi-disciplinary approach, including complementary and alternative medicine. Safety and tolerability of naltrexone in these conditions is supported by the evidence, although evidence of its efficacy is lacking. However, naltrexone has not been described in the literature as a treatment for sickle cell, which shares many characteristics with these other pro-inflammatory conditions. Here we present a case describing addition of naltrexone to a SCD patient's opioid regimen, as well as promotion of a multimodal approach with the patient.

Case Report

A 25 year-old male with past medical history of Hb-SS sickle cell disease presented to our clinic for chronic generalized pain and focal pain in his lower back, left thigh and bilateral shins after moving from out-of-state. He was seen by a primary care physician (PCP) in our health system who prescribed him hydroxyurea, a short course of Percocet, and referrals to pain management and hematology/oncology. No electrophoresis data was available but patient reported both parents have the disease. Patient's pain was largely stable until he was in high school but became exacerbated by athletic and academic pursuits. Patient's symptoms were managed with stretching, heat, and NSAIDs until 2017, at which time he began taking oxycodone and Percocet.

He reported he now has around 4 major sickle cell crises a year which are characterized by pain in his lower back and thighs. His current medications included hydroxyurea 1000mg daily and Percocet 10mg 1-2 tabs every 2 days. However, he reported not taking Percocet for about the previous month since moving to California. He reported that he did not like the way the Percocet made him feel and had been managing his pain with ibuprofen. On physical examination, the patient was found to be athletic without significant findings besides myofascial pain in his lower back.

The patient was started on meloxicam and low-dose naltrexone, given a small supply of Percocet, and instructed to begin a pain diary. A controlled substances agreement was also signed. He was also given referrals for physical therapy and integrative medicine and instructed to follow up with hematology/oncology. The patient was seen via telemedicine by our clinic for follow up about 2 weeks after our initial visit and reported he had been taking 3-4 Percocet 10mg per day over the last 4 days for acute pain and was requesting a refill for 3-4 more days. He reported the pain was worse in the same areas he reported during our initial visit. We recommended he report to the ED as he may be having an acute occlusive crisis and provided him a small refill supply of Percocet. Low dose naltrexone was also discontinued at that time.

Discussion

Chronic pain in SCD can be managed with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) which spare renal function. NSAIDs and vaso-occlusive crises can both lead to kidney damage so patients taking these medications should undergo regular monitoring of renal function. Transcutaneous electrical nerve stimulation (TENS) units, heat therapy, cognitive-behavioral therapy, relaxation techniques, and physical and occupational therapy can be useful in managing chronic pain and maintaining a functional lifestyle. Opioids can also be used in both acute and chronic pain states. Given the inherent issues with opioids as well as NSAIDs, alternative pharmacotherapies should be evaluated.

Recently, new medications, including L-glutamine, an essential amino acid that reduces oxidative stress in sickled red blood cells; crizanlizumab, a monoclonal antibody that inhibits P-selectin, limiting adhesion of HgS and leukocytes to endothelium; and voxelotor, a HgS polymerization inhibitor that blocks the initial step in the production of HgS and works to stabilize oxygenation to reduce sickling of hemoglobin, have been approved for SCD. However, none of these medications provide analgesia during acute pain crises.

Conclusions

Naltrexone presents a promising pharmacotherapy in the treatment of pain in SCD due to its anti-inflammatory properties and potential to deter abuse of other opiates. Further studies are needed to assess effectiveness of naltrexone in treatment of SCD, as well as determining optimal dosing regimens.

Practitioners should also promote a multimodal, multidisciplinary approach that emphasizes maximizing function when treating SCD.

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