

LETTER TO THE EDITOR

Mexiletine: An adjuvant option for refractory pain in patients with sickle cell disease and comorbid autism spectrum disorder

To the Editor:

Sickle cell disease (SCD) is a hemoglobinopathy that causes structural alterations to the beta-globin component of hemoglobin, leading to formation of abnormally rigid, sickle-shaped red cells.^{1,2} This causes recurrent vaso-occlusive crises (VOC) secondary to vessel blockage, ischemia, and microinfarction, manifesting as excruciating pain episodes. The resulting inflammation, necrosis, and nerve damage causes acute pain, but also leads to chronic centralized/neuropathic pain over time.³ Effectively managing pain in this population represents a significant clinical challenge.

Management of acute VOC includes hydration, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For chronic pain, antidepressants (serotonin-norepinephrine reuptake inhibitors or tricyclics) and gabapentinoids may be utilized.⁴ Other recommended therapies include local heat, nerve blocks, physiotherapy, orthopedic intervention, and cognitive behavioral therapy.⁵ When pain fails to respond to these measures, chronic opioid therapy is relied upon.⁶ Opioids may produce hyperalgesia and tolerance with continued use, and carry the risk of respiratory depression and overdose, which is heightened in pediatric patients.⁷ Opioids often serve an essential role in reducing pain to a tolerable level for these patients; however, more efficacious medications with an improved risk and side effect profile are desperately needed.⁸

Optimal pain management requires evaluating pain characteristics, severity, quality, location, aggravating/remitting factors, biopsychosocial factors, effect on function and mood, and comorbidities. Notably, patients with autism spectrum disorder (ASD) often experience sensory abnormalities, which may lead to pain hypo- or hypersensitivity, and may have difficulty describing and localizing pain.^{9–11} We are not aware of any literature addressing pain management in patients with SCD and comorbid ASD.

Lidocaine has been described as a therapeutic option for VOC, however its intravenous (IV) formulation limits its use to inpatient settings given the need for cardiorespiratory monitoring.¹² Mexiletine is akin to an oral version of lidocaine, with a similar mechanism of action. Mexiletine has been shown to improve neuropathic pain, but its efficacy in SCD specifically has not been established.^{13,14} Unsurprisingly, response to IV lidocaine has been found to predict response to mexiletine, likely correlating with the strength of the lidocaine response.¹⁵ Here, we describe a case where an adolescent with SCD (Hgb SC), ASD, and refractory chronic neuropathic/centralized pain was effec-

tively bridged from IV lidocaine to mexiletine with a corresponding decreased opioid requirement.

Our patient is a 19-year-old male with SCD, high-functioning ASD, and numerous hospitalizations for VOC. His outpatient pain plan included short-acting opioids, acetaminophen, nortriptyline, NSAIDs, and methadone. He did not respond to gabapentin or pregabalin. Despite this, he continued with episodes of heightened pain requiring frequent hospitalization. He typically rated his pain 8/10, affecting his chest, right shoulder, and head. He described feeling as though there were “icicles piercing his skin” and “frost inside his skin.” His pain worsened with palpation, suggestive of hyperalgesia, which was thought to be most likely due to opioids given relief of hyperalgesic symptoms from opioid rotations and use of ketamine. While hospitalized, he received hydromorphone patient controlled analgesia, ketamine infusions, numerous integrative medicine therapies, and transcutaneous electrical nerve stimulation, all without lasting benefit. When pain worsened, he would become hypertensive and agitated. His sleep, appetite, and activities of daily living were adversely impacted. He began experiencing more frequent and longer admissions with escalating opioid requirements. During one admission, he developed hypoventilation from opioid toxicity requiring naloxone.

Following this event, a multidisciplinary meeting was held, which included pediatric hematology, anesthesia acute pain service, palliative care, psychology, and pharmacy. His pain plan included acetaminophen 1000 mg three times daily (TID), ibuprofen 800 mg TID, hydromorphone 3 mg every 4 h scheduled and as needed, continuous methadone 10 mg daily and 20 mg twice daily, and a prednisone 40 mg taper. His pain remained poorly controlled. He was then transferred to the PICU for initiation of IV lidocaine given as a 1 mg/kg bolus followed by a 15 µg/kg/min infusion. This was subsequently up-titrated to 35 µg/kg/h based on lidocaine levels over a period of 7 days with dramatic improvement in pain. He had short, intermittent episodes of dizziness and blurry vision, which his mother noted he would often experience prior to admission; however, out of caution his dose was decreased to 30 µg/kg/h.

The lidocaine drip was discontinued at the initiation of mexiletine. The mexiletine was started at 50 mg TID and titrated to 150 mg TID and ultimately 200 mg TID to maintain response prior to floor transfer. He continued to endorse improved energy, sleep, and overall functioning, without need for his as needed opioids. He endorsed a mild headache

4 days after beginning mexiletine, but otherwise felt well. He denied common adverse effects of mexiletine, including dizziness and nausea. His electrolytes and blood counts remained at his baseline, serial EKGs were unremarkable, and an unchanged echocardiogram. He was discharged on mexiletine and remained on this medication for over a year without significant adverse effects.

Lidocaine and mexiletine are use-dependent sodium channel blocking medications. These medications have analgesic properties and efficacy in treating neuropathic pain through, among other mechanisms, inhibiting excitability of dorsal horn neurons and decreasing transmission of pain impulses.¹⁶ In the setting of hypersensitivity to pain experienced by many patients with ASD and the nerve damage known to occur in SCD, these agents may more optimally target the neuropathic and centralized pain component of these disorders. Lidocaine specifically has been demonstrated to be effective for SCD; however, as a cardioactive infusion medication it requires hospitalization for safe administration.¹²⁻¹⁴ Our patient was successfully bridged from IV lidocaine to mexiletine with continued improvement in pain and decreased opioid requirements. Medications for refractory pain that are well tolerated and practical for the outpatient setting would be transformative in improving the quality of life for individuals with SCD and could help reduce pain-related emergency department visits.

This case was complicated by comorbid ASD. Individuals with ASD commonly experience communication challenges, physical disturbances that may persist for extended periods of time, and social isolation.⁸⁻¹⁰ These factors often lead to suboptimal pain treatment. The patient struggled with social isolation, was sensitive about communication, and experienced altered pain processing during times of stress, most notably around school activities. The patient's care was also supported by psychology and psychiatry given his comorbid ASD.

When managing SCD-related pain, it is important to decipher the type of pain that is present, analyze the response to treatment, and choose alternative therapeutic options as needed. Although opioids are certainly necessary in the effective management of acute pain crises, they are not optimal for managing the chronic centralized/neuropathic component of SCD-related pain. Mexiletine appears to show promise as a tool for improving management of refractory centralized/neuropathic pain in SCD, decreasing opioid requirements, and reducing pain-related hospitalizations.

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