Title: Mexiletine: An Adjuvant Option for Refractory Pain in Patients with Sickle Cell Disease and Comorbid Autism Spectrum Disorder

Authors:

Nour K. Kadouh (co-primary)

Department of Clinical Pharmacy, University of Michigan College of Pharmacy

Stacy Lang, MD (co-primary)

Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA

Mark Shamoun, MD

Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA

Eric L. Scott, PhD

Department of Pediatrics; Department of Anesthesiology, University of Michigan Medical School

Sharon A. Singh, MD

Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA

Michael A. Smith, PharmD, BCPS (corresponding author)

Department of Clinical Pharmacy, University of Michigan College of Pharmacy

Adult Palliative Care; F7870 UH South

1500 E. Medical Center Drive

Ann Arbor, MI 48109

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pbc.29526.

Phone: 734-764-5374

Fax: 734-322-3222

Email: mandsmit@med.umich.edu

Word Count:

Main Text – 1094 words

0 Tables, Figures, and Supporting Information Files

Short Running Title: Mexiletine for Refractory SCD Pain

Keywords: Mexiletine, SCD, ASD, chronic pain

SCD Sickle Cell Disease

VOC Vaso-occlusive Crisis

NSAID Non-Steroidal Anti-Inflammatory Drugs

ASD Autism Spectrum Disorder

IV Intravenous

TID Three Times Daily

ED Emergency Department

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, non-steroidal 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 hyper-sensitivity, 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 effectively 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 four hours 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 mcg/kg/min infusion. This was subsequently up-titrated to 35 mcg/kg/hr 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 mcg/kg/hr.

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 ED 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.

References:

1. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010. Published 2018 Mar 15. doi:10.1038/nrdp.2018.10
2. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Adv. 2020;4(12):2656-2701.
3. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med*. 2008;148(2):94-101.
4. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173.
5. Brandow AM, Farley RA, Panepinto JA. Early insights into the neurobiology of pain in sickle cell disease: A systematic review of the literature. *Pediatr Blood Cancer*. 2015;62(9):1501-1511. doi:10.1002/pbc.25574
6. Han, J., Saraf, S. L., Zhang, X., Gowhari, M., Molokie, R. E., Hassan, J., Alhandalous, C., Younge, J., Abbasi, T., Machado, R. F., & Gordeuk, V. R. (2015). *Chronic Opioid Use Pattern in Adult Patients with Sickle Cell Disease.* Blood, 126(23), 3400. Accessed October 09, 2019. Retrieved from http://www.bloodjournal.org/content/126/23/3400.
7. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *The Clinical Journal of Pain.* 2008:24.

8. Sinha CB, Bakshi N, Ross D, Krishnamurti L. Management of Chronic Pain in Adults Living With Sickle Cell Disease in the Era of the Opioid Epidemic: A Qualitative Study. *JAMA Netw Open.* 2019;2(5):e194410. doi:10.1001/jamanetworkopen.2019.4410

9. Xiaosi G, et al. Heightened brain response to pain anticipation in high-functioning adults with autism spectrum disorder. *European Journal of Neuroscience*. Published online May 25 doi:10.1111/ejn.13598

10. Yasuda, Y., Hashimoto, R., Nakae, A. *et al.* Sensory cognitive abnormalities of pain in autism spectrum disorder: a case–control study. *Ann Gen Psychiatry* 15, 8 (2016). https://doi.org/10.1186/s12991-016-0095-1

11. Tudor, ME, Walsh, CE, Mulder, EC. (2015) Pain as a predictor of sleep problems in youth with autism spectrum disorders. Autism 19(3): 292–300.

12. Nguyen NL, Kome AM, Lowe DK, Coyne P, Hawks KG. Intravenous lidocaine as an adjuvant for pain associated with sickle cell disease. *J Pain Palliat Care Pharmacother*. 2015; 29 (4): 359-64. doi: 10.3109/15360288.2015.1082009.

13. Marmura, M.J. Intravenous Lidocaine and Mexiletine in the Management of Trigeminal Autonomic Cephalalgias. *Curr Pain Headache Rep* 14, 145–150 (2010). https://doi-org.proxy.lib.umich.edu/10.1007/s11916-010-0098-6

14. Chabal C, Jacobson L, Mariano A, Chaney E, Britell CW. The use of oral mexiletine for the treatment of pain after peripheral nerve injury. Anesthesiology. 1992 Apr;76(4):513-7. doi: 10.1097/00000542-199204000-00005. PMID: 1312797.

15. Carroll IR, Kaplan KM, Mackey SC. Mexiletine Therapy for Chronic Pain: Survival Analysis Identifies Factors Predicting Clinical Success. *Journal of Pain and Symptom Management.* 2008; 35 (3): 321-326.

16. Olschewski A, Schnoebel-Ehehalt R, Li Y, Tang B, Brau ME, Wolff M. Mexiletine and lidocaine suppress excitability of dorsal horn neurons. *Anesth Analg.* 2009; 109(1):258-64. Retrived from https://www.ncbi.nlm.nih.gov/pubmed/19535719

17. Weiss MD, Macklin EA, Simmons Z, et al. A randomized trial of mexiletine in ALS: Safety and effects on muscle cramps and progression. *Neurology*. 2016;86(16):1474–1481. doi:10.1212/WNL.0000000000002507

18. Lanzkron, S., Carroll, C. P., & Haywood, C., Jr (2010). The burden of emergency department use for sickle-cell disease: an analysis of the national emergency department sample database. *American journal of hematology*, 85(10), 797–799. doi:10.1002/ajh.21807. https://www.ncbi.nlm.nih.gov/pubmed/20730795