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CASE REPORT **OPEN ACCESS**

Marked Opioid Rotation and Multimodal Analgesic Requirement in a Young Adult with Sickle Cell Crisis : A Case Report

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ABSTRACT
Sickle cell disease (SCD) pain management is frequently complicated by significant inter-individual variability in analgesic response. We present the case of a 19-year-old male with homozygous SCD (HbSS) who presented with a severe vaso-occlusive crisis (VOC) that proved refractory to initial therapy. Despite standard hydration and initial dosing with intravenous (IV) tramadol and paracetamol, the patient required rapid escalation and rotation through multiple opioid regimens, including IV pentazocine and a buprenorphine transdermal patch. This case highlights the necessity of individualized, multimodal analgesia and the potential role of buprenorphine in managing refractory sickle cell pain.
Keywords: *Sickle cell disease; Vaso-occlusive crisis; Opioid rotation; Buprenorphine patch; Multimodal analgesia; Pharmacokinetics.*

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INTRODUCTION

Sickle cell disease (SCD) is a global inherited hemoglobinopathy characterized by chronic hemolysis and increased erythrocyte adhesiveness to vascular endothelium.(1) The hallmark of the disease is the acute painful vaso-occlusive crisis (VOC), which is the primary driver of hospital admissions and significantly diminishes quality of life.(2) While opioids are considered the "gold standard" for managing severe pain, concerns regarding tolerance, opioid-induced hyperalgesia (OIH), and variable metabolism often hinder effective analgesia.(3) Achieving adequate relief requires a multipronged approach that incorporates individualized analgesic plans based on the patient's unique physiological requirements.

PATHOPHYSIOLOGY

The pain experienced during a VOC result from a complex synergy of vaso-occlusion, inflammation, and nociception.(1) Deoxygenated hemoglobin polymers cause erythrocytes to sickle, jamming microvascular beds and depriving tissues of oxygen, which leads to ischemia. (5) This environment triggers an ischemia-inflammation cycle where mediators such as endothelin-1 and prostaglandin E2 are released, increasing pain sensitivity.(1)

Furthermore, central sensitization at the level of the spinal cord can cause pain to be perceived in symmetrical or "mirror-image" locations due to viscerosomatic convergence where nerve fibers from different sites meet at the same spinal level.(3)

MOLECULAR MECHANISM AND OPIOID METABOLISM

The transmission of sickle cell pain is modulated by specific receptors within the central nervous system, specifically the AMPA and NMDA channels.(1) While AMPA channels modulate mild-to-moderate stimuli, the NMDA receptor is activated during severe or persistent pain, facilitating central sensitization and glial activation.(1) Opioid metabolism is highly patient-specific and can be influenced by genetic polymorphisms, particularly in the CYP2D6 enzyme.(6) This can lead to ultra-rapid or poor metabolism of certain opioids, resulting in either toxicity or suboptimal pain relief.(3)

Types of Pain in SCD

Sickle cell pain is classified into distinct syndromes: acute recurrent painful crises, chronic pain syndromes, and neuropathic pain.(6-smith) Acute nociceptive pain is the hallmark of VOC, but adult patients frequently develop chronic neuropathic pain as they age.(1) Chronic pain is often defined as pain present on at least

50% of days over a 3- to 6-month period, frequently localized to areas of organ damage like the femoral head.(2)
Additionally, long-term opioid use can lead to opioid-induced hyperalgesia (OIH), where patients become paradoxically more sensitive to minor stimuli, or withdrawal syndromes that may be mistaken for a new crisis.(3)

Description of the Patient

The patient is a 19-year-old male with homozygous SCD (HbSS) who presented with severe right lower limb pain lasting two days. He was maintained on hydroxyurea and folic acid and had no history of previous blood transfusions. Upon examination, he appeared in poor general condition due to the intensity of his pain. Laboratory results confirmed active hemolysis with a hemoglobin of 10.6 g/dL, elevated LDH (775 U/L), and indirect hyperbilirubinemia rising to 4.1 mg/dL. Renal and hepatic parameters remained within normal limits.

Treatment and Multi-Drug Administration

The patient's hospital course required a rapid transition through several analgesic modalities to achieve pain control. Initial treatment with IV tramadol and paracetamol provided only partial relief, necessitating the addition of IV pentazocine. On the third day, a buprenorphine transdermal patch was applied to provide more stable, sustained analgesia. Pain was eventually controlled through this multimodal approach, which also included etoricoxib and continued hydroxyurea.

Table 1: Summary of Analgesic Interventions

Day Analgesic & Adjuncts Clinical Remarks

Day	Analgesics & Adjuncts	Clinical Remarks
1	IV Tramadol 100 mg BD + IV Paracetamol 1 g BD	Partial relief of severe limb pain.
2	IV Pentazocine 30 mg SOS	Moderate response; used as rescue analgesia.
3	Buprenorphine Transdermal Patch (5 µg/hr)	Applied for improved, sustained pain control.
4	Etoricoxib 90 mg OD + Hydroxyurea 500 mg BD	Pain adequately controlled with multimodal therapy.
5	Shifted to oral analgesics	Discharged; pain score improved from 8/10 to 2/10.

DISCUSSION

The management of this 19-year-old patient illustrates the pharmacological complexity encountered during the transition from adolescence to young adulthood in SCD. At this age, patients often reach a peak in the frequency of painful crises, and their pain patterns may shift from acute episodic nociceptive pain to persistent or centralized pain syndromes (1).

Pharmacokinetic and Pharmacogenetic Variability

The patient's initial "pharmacoresistance" to IV tramadol may be explained by altered opioid metabolism. Chronic inflammation in SCD increases cytokines such as IL-6 and TNF-alpha, which can alter hepatic enzyme activity and reduce opioid clearance, leading to unpredictable plasma levels.(3) Furthermore, genetic polymorphisms in the CYP2D6 enzyme significantly influence the response to opioids.(6) Patients identified as "poor metabolizers" cannot efficiently convert pro-drugs into active metabolites, resulting in suboptimal analgesia, whereas "ultra-rapid metabolizers" are at risk for toxicity from rapid conversion (3).

Molecular Mechanisms of Refractory Pain

When pain becomes severe or persistent, the molecular modulation of stimuli shifts from the AMPA channel to the NMDA receptor (1). Activation of the NMDA receptor facilitates central sensitization and glial activation, which are key drivers of opioid tolerance and OIH.6 The patient's requirement for multiple opioid rotations reflects a strategy to overcome receptor desensitization. The use of pentazocine, a mixed agonist-antagonist, requires caution as it can potentially blunt the analgesic effect of pure mu-agonists or precipitate withdrawal symptoms in opioid-dependent patients (3).

The Role of Buprenorphine and Multimodal Therapy

The successful integration of a buprenorphine transdermal patch provided the patientwith sustained, stable analgesia. Buprenorphine is considered a potential candidate for treating persistent sickle cell syndromes .(7) Combining this with hydroxyurea was essential; hydroxyurea acts as a disease modifier by inducing fetal hemoglobin (Hb F), which reduces red blood cell adhesion and neutrophil activity, thereby shortening the duration of crisis-related admissions (1).

CONCLUSION

Managing pain in a sickle cell crisis requires early recognition of inadequate response and the rational use of opioid rotation. This case demonstrates that multimodal therapy and personalized pharmacological strategies are essential for achieving adequate relief in refractory cases. The transition to a buprenorphine transdermal patch in this 19-yearold patient demonstrated that long-acting partial agonists can successfully manager factory pain without the serious medical side effects often associated with high-dose pure agonists**.(7)** Ultimately, the integration of personalized pharmacotherapy and early recognition of inadequate analgesic response are critical for improving outcomes and minimizing opioid toxicity in patients with sickle cell disease.

Learning Points

- Sickle cell crisis pain can exhibit opioid pharmacoresistance requiring rotation.
- Mixed agonist–antagonist opioids (like pentazocine) should be used cautiously after pure agonists.
- Buprenorphine transdermal patches may be beneficial for sustained analgesia in refractory cases.
- Monitoring bilirubin and LDH is essential to assess ongoing hemolysis during a VOC.
- Personalized strategies, including pharmacogenomics, represent the future of SCD pain management.

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CONFLICT OF INTEREST

The author declares no conflict of interest related to this study.

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