PALLIATIVE CARE
CASE OF THE MONTH

"Opioid-induced Hyperalgesia"
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Case: SM is a 25-year-old female with rhabdomyosarcoma that unfortunately progressed despite multiple rounds of chemotherapy and surgery. She presented to the emergency department with worsening of her chronic tumor-related abdominal pain and new, diffuse pain of the muscles and joints. Her mother reported SM had been experiencing episodes of confusion and hallucinations over the past week. Her home pain regimen of long-acting morphine and as needed oxycodone had been titrated aggressively over the past month to very high doses (600 oral morphine equivalents) in an attempt to control her pain.

When first evaluated by the palliative care consult service, she was in severe distress. She described severe, 10/10, diffuse pain. On exam there was generalized tenderness of the abdomen, as well as her shoulders, upper legs, and lower back. She was exhibiting myoclonic jerks of her upper extremities every 3-4 seconds. Although she was alert and oriented, she was easily distracted during the exam and required frequent redirection.

Our palliative care team was concerned about opioid-induced hyperalgesia (OIH). Suspicion was high given the paradoxical worsening of her pain despite high doses of opioids and the neuroexcitatory signs and symptoms (myoclonus, confusion, and hallucinations) she was exhibiting. Therefore, it was decided to lower the overall dosage and switch her opioid regimen in an attempt to reverse OIH. Her long-acting morphine was discontinued and replaced with methadone 5mg three times per day. Her as-needed oxycodone dose was reduced from 30mg to 5mg every 4 hours. To control the myoclonus, low dose lorazepam was administered three times per day.

Discussion: Opioid-induced hyperalgesia (OIH) is a rare syndrome of increasing pain, often accompanied by neuroexcitatory effects, in the setting of increasing opioid therapy. Clinicians should consider OIH in patients on high dose opioids or during a period of rapid opioid escalation. While case reports show a wide range of dosages can provoke this syndrome, the majority of patients are on very high doses, often >1000mg oral morphine equivalents per day and typically via parenteral routes (IV and intrathecal). Morphine is by far the most common opiate implicated in OIH. Hydromorphone and oxycodone, members of the same class of opiate as morphine (phenanthrenes), can also cause OIH, but oxymorphone has not been shown to cause it. Methadone, a synthetic opioid in the class of diphenylheptanes, and fentanyl, a synthetic opioid in the class of phenylpiperidine, are less likely to precipitate OIH.

Existing data suggests that OIH is caused by multiple opioid-induced changes to the central nervous system including:
-Activation of N-methyl-D-aspartate (NMDA) receptors
-Inhibition of the glutamate transporter system
-Increased levels of the pro-nociceptive peptides within the dorsal root ganglia
-Activation of descending pain facilitation from the rostral ventromedial medulla
-Neuroexcitatory effects provoked by metabolites of morphine and hydromorphone

OIH can be confused with tolerance as in both cases patients report increased pain on opioids. The two conditions can be differentiated based on the patient's response to opioids. In tolerance, the patient's pain will improve with dose escalation. In OIH, pain will worsen with opioid administration. This paradoxical effect is one of the hallmarks of the syndrome.

On physical exam, patients are grimacing in pain with moderate-to-severe distress, myoclonus, altered mental status or delirium and often allodynia (pain due to non-painful stimuli, such as light touch).

Typically, if you suspect OIH, you should get a pain or palliative care consultation because it will seem wrong to decrease opiates in a patient in severe pain. Opiate dose reduction and rotation to a synthetic opioid such as fentanyl or methadone is recommended. Methadone has the additional benefit of NMDA antagonism. It is not surprising that methadone has been shown to improve or resolve OIH given the role NMDA activation plays in causing OIH. Adjuvant therapies, such as acetaminophen or neuropathic pain medications, should be considered as they may decrease the need for opioids. Benzodiazepines may be a temporary addition to manage myoclonus as the OIH resolves.

Symptoms of OIH do resolve when patients are treated with the above strategies. However, it can be long and difficult to wean some patients to a low enough level of opioids to stop OIH. Existing literature does not address any long-term consequences of OIH. We hope to see more research on this subject.

Follow up:
Over the next 48 hours in the hospital, her myoclonus improved. Her pain and mental status improved more slowly. It took a week to re-establish control of SM's pain. At the time of discharge, she rated her pain as 3/10. Her new pain regimen consisted of methadone 10mg three times a day and oxycodone 5mg every 4 hours as needed.

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the *Palliative Care Program at PUH/MUH*, 647-7243, beeper 8511, *Shadyside Dept. of Medical Ethics and Palliative Care*, beeper 412-647-7243 pager # 8513, *Perioperative/ Trauma Pain* 647-7243, beeper 7246, *UPCI Cancer Pain Service*, beeper 644 –1724, *Interventional Pain* 784-4000, *Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore* and Children's page 958-3844. With comments about "Case of the Month" call Dr. Robert Arnold at (412) 692-4834.

References:

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