INSTITUTE TO ENHANCE PALLIATIVE CARE

PALLIATIVE CARE CASE OF THE MONTH

"When pain gets worse despite escalating narcotic doses"

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Case: The patient was a 33-year-old woman with recurrent carcinoma of the cervix. Her course was complicated by abdominal pain and development of an entero-vaginal fistula. On exploratory laparotomy she was found to have extensive peritoneal metastases with several areas of small bowel involvement. A diverting jejuno-ileostomy was performed. Postoperatively, her gynecologic oncologist told the patient and her husband that her cancer was not resectable. He recommended the patient go home with hospice after recovery from surgery.

Prior to surgery, the patient's pain had been well controlled with transdermal fentanyl 125 mcg/hr and oral hydromorphone as needed for breakthrough pain. Post-operatively, transdermal fentanyl was continued at 125mcg/hr. Patient-controlled analgesia (PCA) with intravenous hydromorphone, 1mg per bolus dose, was initiated for breakthrough. On her first post-operative day, the patient used an average of 3mg of hydromorphone per hour and still had significant incisional and abdominal pain. A continuous rate of 3mg/hour was added to her PCA with 2mg demand doses as needed. The patient's pain persisted, and on the second post-operative day, she used an average of 7mg/hour of hydromorphone. Her continuous rate was increased to 4mg/hour.

On the third post-operative day, the patient used an average of 10mg/hour of hydromorphone over a 12-hour period. She reported 9/10 incisional pain. Her nurse noted that she was exquisitely tender to light touch on the skin over her abdomen. Examination revealed a healing incision without erythema, edema or purulent discharge. The patient was guarding the area around the incision with her hands and would not allow the examiner or even the bed sheets to touch that part of her skin. She was in moderate distress secondary to pain. No myoclonus was noted and the patient denied any abnormal movements of her hands or feet. She was alert and oriented and denied hallucinations.

The diagnosis of opioid-induced hyperalgesia was made based on the patient's report of pain resulting from ordinarily non-painful stimuli (allodynia) and her increasing incisional pain despite dramatic increased dose of narcotics. Hydromorphone was discontinued and the patient was started on methadone 60mg orally three times daily with IV fentanyl PCA, 40mcg per bolus dose, for breakthrough pain. Her allodynia resolved and her pain control improved to a level of 2 to 3 out of 10. She was discharged to home hospice on that regimen.

Discussion: Opioid-induced hyperalgesia, or paradoxical pain, is a poorly understood clinical syndrome that some pain experts believe has become increasingly common as clinicians are more aggressively treating pain with high-dose opioids[4]. Although controversy exists as to what causes the syndrome, the clinical picture has been well described in the medical literature. Patients develop a lower pain threshold, or hyperalgesia, as well as allodynia while receiving narcotics for pain. These symptoms paradoxically get worse as the opioid dose is increased. Some patients develop other hyperexcitability effects of opioids including myoclonus and seizures. This clinical syndrome can be differentiated from opioid tolerance by the presence of pain that becomes more diffuse and severe on increasing doses of narcotics. Although opioid tolerant patients also use increasing doses of narcotics, their pain does not increase over baseline unless their narcotic dose is decreased.

Several mechanisms have been proposed for the etiology of opioid-induced hyperalgesia. These include the hypothesis that opioid metabolites, such as morphine-3-glucuronide (M3G) or hydromorphone-3-glucuronide (H3G), directly cause the constellation of symptoms. Another theory is that central sensitization occurs as a result of opioid-related activation of N-methyl-D-asparate (NMDA) receptors in the central nervous system. Other experts on pain management feel that the syndrome is not opioid toxicity at all, but rather opioid-poorly-responsive pain complicated by delirium and hyperexcitability. [1]

Despite controversy over the etiology of opioid-induced hyperalgesia, therapies for the syndrome remain the same. They include rotating the patient to another opioid, preferably one that does not metabolize to M3G or H3G such as fentanyl or methadone. Methadone is also felt to be helpful because it antagonizes NMDA receptors. Another approach is to decrease the current opioid dose and add in infusion of a non-narcotic NMDA receptor antagonist such as ketamine. [2] [3] If these therapies fail, epidural or intrathecal anesthesia has also been found to be effective in case reports. [4]

In conclusion, when treating patients for pain with high dose narcotics, it is important to pay close attention to patients who report increasing pain despite increasing doses of narcotic. Given the complexity of the therapies for this syndrome, a referral to a pain or palliative care clinician is often indicated when opioid-induced hyperalgesia is suspected.

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[1] Portenoy RK, Forbes K, Lussier D, Hanks G (2004). Difficult pain problems: an integrated approach. In *Oxford Textbook of Palliative Medicine* 3rd edn (ed. Doyle D, Hanks G, Cherny N, Calman K), p. 439. Oxford: Oxford University Press.

[2] Laird D, Lovel T. Paradoxical pain (letter). Lancet 1993; 341: 241.

[3] Walker SM, Cousins MJ. Reduction in hyperalgesia and intrathecal morphine requirements by low-dose ketamine infusion (letter). J Pain Symptom Manage 1997; 14:129-133.

[4] Mercadante S, Ferrera P, Villari P, Arcuri E. Hyperalgesia: An emerging iatrogenic syndrome. J Pain Symptom Manage 2003; 26: 769-775.

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