Monika Patel, M.D., Lakshmi Koyyalagunta, M.D., and Mitchell Engle, M.D., Ph.D.
Department of Pain Medicine
MD Anderson Cancer Center
Texas Pain Society Case Report

The Intersection of Opioid Induced Hyperalgesia, Tolerance and Disease Progression

Introduction: The unripened seed capsules of *Papaver Somniferum* have been used for analgesia since ancient times[1]. However, despite their highly effective analgesic effect, repeated use can lead to opioid tolerance, dependence, and the phenomenon of opioid induced hyperalgesia (OIH)[3]. OIH is defined as a paradoxical response to opioid administration that causes increased sensitivity to pain[4]. This is a presentation of treatment strategies used in a case of OIH, tolerance, and cancer disease progression.

Case Report: A 47 year old female with a recent diagnosis of metastatic gallbladder cancer presented from an outside hospital. She had a two month history of opioid use and dose escalation resulting in usage of over 2,500 mg morphine equivalent daily dose (MEDD) from methadone, morphine sulfate extended release, and morphine sulfate immediate release usage. She complained of poor pain control. Physical exam did not follow a clear pattern, showing a non-tender abdomen, diffuse allodynia over the left lower extremity, and diffuse muscle tenderness. We concluded she had developed OIH and recommended an opioid weaning schedule. At her follow-up visit one month later, she was able to wean herself off morphine sulfate extended release decreasing her MEDD to approximately 2,000 mg with continued methadone and morphine sulfate immediate release usage. In addition, her OIH had improved with decreased diffuse pain, but she had developed new onset increased pain localized to the midline and paraspinal T5-T7 region. Computerized Tomography of the chest showed metastatic disease progression causing a pathological fracture at the T6 vertebral body, and radiation therapy was planned. Given her high level of opioid tolerance, focal disease progression with associated localized pain, and the absence of diffuse myalgias, her methadone dose was increased. In addition, several adjuvant agents such as lidocaine 5% patches, duloxetine, haloperidol and gabapentin were started to decrease her opioid requirements. She was subsequently able to wean to a MEDD of approximately 1,000 mg.

Discussion: Although OIH is not fully understood, rodent studies have demonstrated that high dose opioids can produce hyperalgesia, allodynia, and motor excitation[1]. The morphine metabolite morphine-3-glucuronide (M3G) may play an important role in this process. In human observational cohort studies, OIH positively correlates with increasing opioid dose and duration of opioid treatment[5]. In general, OIH can be treated by weaning opioids, particularly morphine as was done in this case. Like OIH, tolerance is a complex biological process. However, it is defined by improved pain control with opioid dose escalation. Again, rodent studies have demonstrated that it may be mediated by modulation of cytokine expression, which can be reversed by the coadministration of gabapentin[2]. In addition, haloperidol has been shown to attenuate the anti-nociceptive tolerance to morphine[3]. In this case, adjuvant treatment with gabapentin and haloperidol resulted in a decreased opioid requirement.

Conclusions: OIH, opioid tolerance, and disease progression can be difficult to distinguish from one another in complex patients. After the elimination of disease progression as a reason for increased pain, decreased or less than expected effects from opioids is due to either tolerance or OIH. The simple test to distinguish the two is by increasing opioid dose which will result in pain reduction in a tolerant patient but not in a patient with OIH. In this case, the patient presented with all three states over the course of treatment and appropriate opioid and adjuvant modulation was performed to produce a satisfactory clinical outcome.

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