

# Is Mechanism and Symptom-Based Analgesia an Answer to Opioid-Induced Hyperalgesia?

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### ABSTRACT

“Cancer Pain” and “Pain in cancer patient” are not synonymous. Opioid-induced Hyperalgesia (OIH) is a paradoxical state of nociceptive sensitization caused by exposure to opioids. Neuropathic pain is only partially responsive to opioids; injudicious increase in dose of opioids in neuropathic pain may not only result in inadequate pain relief but also OIH. Majority of literature on OIH is in non-cancer pain with systemic use of opioids. We describe the development and successful treatment of OIH in a 55-year-old male patient with Small cell Carcinoma Lung. Opioid tapering, rotation, systemic desensitization helps in combatting OIH. The use of anti-neuropathic adjuvant analgesics helps not only in preventing and treating OIH but also in understanding putative mechanisms underlying neuropathic pain and OIH.

**Key words:** Mechanism based, opioid induced hyperalgesia, opioids

### INTRODUCTION

Pain is the most common and multifactorial symptom of cancer. Opioids are considered as the cornerstone of cancer pain management. Opioid Induced Hyperalgesia (OIH) is a paradoxical state of nociceptive sensitization caused by exposure to opioids.<sup>[1]</sup> The incidence, predisposing factors and underlying mechanisms remain largely unknown.<sup>[1-4]</sup> Neuropathic pain is only partially responsive to opioids;<sup>[5]</sup> injudicious increase in dose of opioids in neuropathic pain may result in OIH. Adjuvant analgesics by supplementing analgesia and avoiding injudicious increases in opioid doses not only herald OIH but also prove to be a valuable treatment tool in OIH. In literature, OIH has mostly been described in non-cancer pain with systemic use of opioids.

### CASE REPORT

A 55-year-old male known case of metastatic small cell carcinoma lung was admitted for severe pain over right buttock with pain and tingling sensation in right leg and sole. Whole body 18F fluorodeoxyglucose (FDG) positron emission tomography computer tomography (PET-CT) scan depicted hypermetabolic lytic/sclerotic lesions in multiple skeletal regions including cervico-dorso-lumbar vertebrae and bilateral pelvic bones. Magnetic resonance imaging (MRI) spine revealed multiple areas of marrow signal alteration suggesting metastasis in almost all the visualized vertebrae. Ventral epidural soft tissue was seen at right S1 compressing right traversing nerve root.

Patient was prescribed Tablet Morphine sulphate Immediate Release (IR) 10 mg 4 hourly, injection diclofenac 50 mg intravenous (iv) tds and injection zoledronic acid iv every 4 weeks for persistent back pain. Morphine was escalated to 15 mg followed by 20 mg 4 hourly and SOS over 48 hours in view of unremitting pain. Despite increase in morphine dosage, pain increased both in intensity and distribution. Patient developed pain, burning, and tingling sensation in bilateral legs which used to increase 30 minutes to an

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hour after ingestion of oral morphine. The patient was referred to our pain clinic. A complete history and physical examination including neurological and musculoskeletal examination was performed. Patient had sharp, shooting pain in right buttock radiating to right lower limb till sole of the foot (*S1 radiculopathy*) and burning pain in bilateral lower limbs with a 10-point visual analogue score (VAS) of 9/10 with a minimum VAS of 8/10. Pain was neuropathic in nature (Pain Detect Tool score of 19). Examination revealed bony tenderness present over multiple dorso-lumbar spinous processes and right sacral region and allodynia in bilateral lower limbs. Rest of the neurological examination was normal except for the right side ankle reflex which was absent. Tablet Morphine was tapered to 10 mg 4 hourly and 10 mg SOS, Buprenorphine patch 20 µg/hour was applied and Inj Dexamethasone 8 mg intravenously BD was started to reduce the edema. However, patient refused to take oral morphine due to increased pain and burning sensation associated with its consumption. Injection Tramadol 50 mg intravenous TDS was started to tackle ongoing pain. Injection Lignocaine 3 mg/kilogram body weight (BW) and injection ketamine 0.2 mg/kilogram BW diluted in 100 ml normal saline was given intravenous slowly over 1 hour consecutively for 3 days, under electrocardiography (ECG), Noninvasive blood pressure (NIBP) and Pulse oximeter (SPO<sub>2</sub>) monitoring. The patient did not develop side-effect other than mild dizziness and demonstrated reduction in pain and burning sensation after each infusion; however, the effect was short lived. Analgesia was supplemented with Tablet Etorocoxib (Cox-2 inhibitor) 60 mg BD and injection Paracetamol 1 gram iv TDS. Tablet Gabapentin-NT 1 tablet HS was started and escalated gradually to BD and then TDS to tackle neuropathic component. Radiotherapy to the lumbosacral region was started and continued for 5 days. Patient's intensity of pain decreased to 1/10, allodynia and hyperalgesia decreased. Over next few days Nucoxia and tramadol were stopped, inj Paracetamol converted to tablet paracetamol 1 gram TDS. The analgesia was maintained successfully and patient discharged on Buprenorphine patch 20 µg/hour and tablet Gabapentin-NT TDS.

## DISCUSSION

OIH is diagnosed when increase in opioid doses causes escalating pain intensity or distribution or both.<sup>[3]</sup> There may be associated allodynia or hyperalgesia which may be so severe that even non painful stimulus such as touching, clothing, pressure, or heat produces excruciating pain. Its diagnosis may be confounded by factors such as worsening pain pathology or opioid tolerance; which

unlike OIH usually respond to increase in opioid dosage. Neuroplastic changes such as upregulation of N Methy D Aspartate (NMDA) receptors, windup, descending pain facilitation, enhanced production, and decreased breakdown of excitatory neurotransmitters have been postulated as the underlying mechanisms of OIH.<sup>[2,3]</sup> Ketamine, a NMDA receptor antagonist, in subanaesthetic doses suppresses NMDA receptor mediated neuronal plasticity and its clinical correlates such as allodynia and hyperalgesia.<sup>[1,6]</sup> Lidocaine, a local anesthetic and Na channel blocker is effective in a number of neuropathic pain conditions.<sup>[7]</sup> Cycloxygenase-2 (COX-2) selective antagonists inhibit spinal release of excitatory neurotransmitters (glutamate), prostaglandins, and may partially reverse OIH. Buprenorphine due to its action as kappa antagonist- and voltage-gated Na channel blocker has been found to be useful in neuropathic pain and hyperalgesia.<sup>[8-10]</sup> Tramadol likely due to its inhibitory action on serotonin and norepinephrine reuptake is useful in neuropathic pain.<sup>[11,12]</sup> Systemic desensitization with Injection lignocaine, ketamine, and opioid rotation, helped in reversing OIH. These in combination with COX-2 inhibitors, acetaminophen, gabapentin, and nortryptiline helped in controlling pain by the time palliative radiotherapy reduced the mass effect. Accurate determination of pain generating mechanism is complex but essential for a rational analgesic therapy. A top-down approach in delineating neuropathic pain mechanism may prove to be a daunting task because of heterogeneity of pathophysiologic mechanisms in different pain states but also in different patients. In such a scenario, a bottom-up approach of selecting anti-neuropathic medications based on patients symptomatology may prove not only gratifying but also in understanding putative neuropathic mechanism involved in that patient. It is important not to have a tunnel vision when treating a patient with cancer pain. The diagnosis of neuropathic pains though not a deterrent but warrants judicious use of opioids along with co-analgesics. Tailoring analgesic prescription to algesic mechanism, repeated assessment to evaluate analgesic effectiveness, side-effects, and continued search for pain generating mechanism are the analgesic pillars, importance of whom cannot be emphasized enough.

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