Intractable Post Operative Pain Resulting in Opioid-induced Hyperalgesia and Subsequent Serotonin Toxicity

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Introduction

We report on a 31-year-old female with a medical history of Crohn’s disease, depression, anxiety, and fibromyalgia who presented as a consult to the acute pain service with uncontrolled pain after laparoscopic subtotal colectomy. She was initially started on a home pain regimen that included oxycodone and duloxetine with the addition of a hydromorphone PCA. She continued to complain of increasing pain with increasing doses of opioids and opioid rotation. On post-operative day 16 she was diagnosed with serotonin syndrome, and that evening she became somnolent requiring multiple doses of naloxone. At that point she was taken off opioids and duloxetine. After approximately three days of being on low dose opioid therapy (about 25% of pre-surgery dose) her symptoms of serotonin syndrome resolved and her pain was tolerable. She was subsequently discharged on post-operative day 21. Our patient’s pain progression is consistent with opioid-induced hyperalgesia, wherein acute high dose or chronic low dose opioid administration leads to a paradoxical state of heightened pain sensitivity. The escalating opioid dosing not only led to opioid-induced hyperalgesia but also, in combination with duloxetine, ondansetron, and poor nutritional status, contributed to the onset of serotonin syndrome.

Opioid-induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is characterized by a paradoxical response in heightened pain sensation in which both pain threshold and pain tolerance decrease. OIH is similar to opioid tolerance in that opioid drugs exhibit diminished efficacy with time; however, OIH differs from tolerance in that dose increases are associated with increased pain sensitivity and higher pain scores. While the precise mechanism of OIH is not understood many different mechanisms have been studied including central pain sensitization, spinal dynorphin release, NMDA receptor activity, NMDA antagonists, α2 agonists, non-steroidal anti-inflammatory drugs, GABA analogues, as well as opioid rotation have been shown to decrease OIH.

Serotonin Syndrome

This patient had an ongoing diagnosis of anxiety and depression. Upon initial evaluation by the psychiatry team on post-op day 15 she had symptoms of increased anxiety, agitation, delirium, somnolence, myoclonus, rigidity, poor memory with circumstantial thought process. The medications that she had been taking that could contribute to serotonin toxicity included: methadone, oxycodone, hydromorphone, duloxetine, ondansetron. In regards to duloxetine, which is a drug that is >90% plasma protein bound, she had been NPO for approximately two weeks and her prealbumin level near the time of diagnosis was 8 (17–39).

In regards to the opioid medication and role in serotonin syndrome, many different opioids have been implicated. The mechanism by which these drugs are believed to be serotonergic include a weak serotonin reuptake inhibition and an increase release of intrasynaptic serotonin. The synthetic piperidine opioids (fenatanyl, methadone, meperidine) act by both mechanism of reuptake inhibition and increased serotonin release. The phenantherene morphine analogs (oxycodone, hydromorphone, oxymorphone) act only by increasing release of serotonin.

As of 2003 the Hunter Serotonin Toxicity Criteria was adopted as this was found to be more sensitive and specific than pre-existing Steinbach Criteria.

Hunter Serotonin Toxicity Criteria: Decision Rules

*In the presence of a serotonergic agent:
1. If (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE if (inducible clonus = yes) AND [agitation = yes OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE if (ocular clonus = yes) AND [agitation = yes OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE if (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE if (hypertonia = yes AND temperature > 38°C) AND (ocular clonus = yes OR inducible clonus = yes) THEN serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

Discussion

Our patient, with a history of chronic pain, was taking 30 oral morphine equivalents (OME) daily prior to laparoscopic subtotal colectomy. On post-op day one she was continued on her home pain medication plus a dilaudid PCA, for a total of approximately 100 OMEs. On post-op day 16 she was diagnosed with serotonin syndrome, at this time she was taking 600 OMEs and 15 mg tid PO methodone. Two days after being diagnosed with serotonin syndrome, and after discontinuing duloxetine and stopping all narcotics with the exception of her initial home medication of 30 OMEs, the serotonin toxicity had resolved and her pain state was tolerable.

Multiple techniques were attempted to decrease opioid consumption including the addition of NSAIDS, pregabalin, and opioid rotation, all of which have been proven to help reduce the risk of OIH. However, the only thing that proved beneficial was drastically decreasing opioid dosage. While serotonin toxicity and opioid-induced hyperalgesia are independent conditions, there is no question that continued dose escalation without improvement of pain was involved in the onset of serotonin syndrome. Understandably the strongest contributor to serotonin toxicity in this patient was the continued use of duloxetine with poor nutritional status, but the opioid medications played a key part.

As physicians and prescribers of pain medicine we must be aware of OIH and develop an automatic reaction when a patient complains of worsening or no improvement with dose increase. This reaction should be to decrease their dose rather than increase further. While the patient may not be agreeable to this plan it is my opinion that our patients would benefit more with dose reduction.

References