CASE REPORT

Opioid-induced hyperalgesia: when pain killers make pain worse

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SUMMARY

A 44-year-old woman had a temporal glioma and was admitted to the hospice with pain that was not controlled despite escalating opioids. Her pain levels rose after every dose increase resulting now in continuous pain, making her very low in mood. Her short-term memory had also declined in a stepwise fashion with each increase in opioids. Additionally, her poor health had had a detrimental effect on family life. Physical examination was difficult due to allodynia but no major abnormality was found. The team suspected opioid-induced hyperalgesia and decided to cut the patient's opioids by one-third initially. This immediately improved the overall pain. The opioids continued to be decreased incrementally every 1–2 days until the pain had disappeared completely. She was stabilised on a dose almost one-seventh of her original regime. Mood and memory also improved as opioids decreased and she was discharged home after 8 days.

BACKGROUND

Opioid-induced hyperalgesia is a rare but increasingly recognised cause of pain in a population established on strong pain killers. As this population grows, more and more cases are being identified. It is difficult to recognise and often these patients are mistaken as being opioid dependent or having worsening primary disease.

CASE PRESENTATION

Our case is of a 44-year-old housewife. She lives with her children and her husband, who is her main carer. She was diagnosed in 2010 with a temporal glioma. This transformed into a high-grade glioma in 2012 and the patient was referred to specialist palliative care services and has since been going to St Wilfrid's Hospice. She initially presented to an outpatient appointment via the Day Therapy Unit with symptoms of sharp pain on a background of constant dull pain which had developed over 5 weeks. This mainly affected the left arm, shoulder and back but other areas of her body were intermittently implicated. Despite rapidly escalating doses of oxycodone by her general practitioner during this time, her husband noted the pain was discriminately worse following each rise. As her pain was not being managed effectively in the community she was admitted to the hospice for treatment.

She had pain 'all over' her body. She was unable to get into a comfortable position, even light touch and contact with the bed sheets caused a burning pain. In particular, she had constant pain down the

full length of her left arm, shoulder and back which was exacerbated by any movement. Her jaw was very tense and protruded. She had also had falls recently, unpleasant auditory and visual hallucinations and her husband was concerned her short-term memory had deteriorated with every increase in pain medications. Her current pain medication was long-acting oxycodone 55 mg twice daily, oxycodone 20 mg four times a day, codeine phosphate 60 mg three times a day and paracetamol 1 g four times a day, none of which provided any relief.

The patient's medical history included headaches, seizures and hypothyroidism; her other medications were levothyroxine 25 µg, carbamazepine 600 mg twice daily and levetiracetam 1.5 g twice daily, movicol 1 sachet three times a day, sodium docusate 300 mg three times a day, lansoprazole 15 mg twice daily and metoclopramide 10 mg three times a day. These medication doses had all been stable for over 3 months.

The patient was living downstairs, with the family living room being semiconverted into her bedroom. Since the worsening of her symptoms she had become house-bound and relations between herself and her teenage children had become fraught. Her husband was also struggling with the increase in care requirements. This had created stress within the home environment which had a knock-on effect on her mood.

Examination was difficult due to allodynia, but grossly normal. Neurological examination showed tense masseters and temporalis muscles bilaterally with all other cranial nerves intact and upper limb weakness of 3/5, with left side worse than right, compared with 5/5 power in lower limbs.

INVESTIGATIONS

Latest blood tests 3 weeks previously showed FBC, U&E, calcium and LFTs were all within range. MRI of the brain performed in the previous month showed the tumour was static.

DIFFERENTIAL DIAGNOSIS

Patients with chronic pain on strong opioids involve a wide range of primary diagnoses. This includes, but is not limited to, patients with cancer, musculoskeletal problems and rheumatological diseases. Often an increase in pain in these patients is related to worsening of their primary disease and this must be investigated appropriately. Often pain of this nature is localised and responds to an increase in pain relief. Similarly, opioid tolerance will present as an increase in pain in the previously

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localised area and respond appropriately to an increase in dose. Both are of gradual onset.

Conversely, opioid withdrawal may present with a short onset of diffuse pain but again will respond well to increases in opioid doses. In the case of opioid tolerance and withdrawal in patients addicted to opioids without pre-existing disease their symptoms respond well to increase in opioids but often with a functional deficit, for example, drowsiness, hallucinations, low respiratory rate, etc.

In opioid-induced hyperalgesia the key differential marker is that pain does not improve despite the increase of opioid dose, and therefore patient history is vital to its correct diagnosis. Within all of these diagnoses it is important to evaluate the contribution of low mood and anxiety to the somatisation of pain. It is well documented that patients with chronic diseases suffer from depression and anxiety and this can compound symptoms. Therefore this should also be concurrently treated. Patients can find it difficult differentiating between chronic pain and novel causes of pain such as headaches and muscular aches and therefore use of opiates for different aetiology pain can happen. Also interactions between drugs can compound their efficacy, in this case the potential interaction between carbamazepine decreasing oxycodone levels by interfering with CYP3A4 metabolism.

TREATMENT

There are several options in treating opioid-induced hyperalgesia. We chose a combination of reducing current opioid intake in a controlled fashion and employing non-opioid therapies to distract from pain.

Overall opioid intake was decreased initially by one-third—from oxycodone 200 to 130 mg—distributed in regular doses every 4 h. This made titrating down the dose easier to control over the proceeding days. Every 1–2 days the 4 hourly doses were decreased by 5 mg as the patient tolerated.

In addition to reducing the opioids, distraction therapy was used to help patient find other ways of controlling the pain than resorting to opioids. Complementary therapy and counselling were also employed to add structure to the patient's day and help take her mind off pain. Nursing staff attempted to help the patient identify causes of pain and localising where it was instead of saying 'all over' pain. Alternative drug therapies initiated during the admission were lorazepam for anxiety/muscular tension which helped significantly resolve the pain caused by jaw protrusion, thought to be a physical response to anxiety.

Other pharmacological options include opioid rotating. Incomplete cross-tolerance allows for some reduction in dose for an equianalgesic effect. This often shows promise but is still prone to eventual opioid-induced hyperalgesia with the second agent. Other effective therapies include switching to a non-opioid adjuvant, such as ketamine or methadone. These employ N-methyl-D-aspartate (NMDA)-receptor signalling as opposed to opioid receptors and therefore cannot result in hyperalgesia by the same mechanism. Both require tightly controlled titration in specialist settings.

OUTCOME AND FOLLOW-UP

The patient was stabilised on oxycodone 5 mg every 4 h. There was a dramatic decrease in the patient's subjective pain description as the opiate dose decreased and she was much more comfortable. The reduction in pain levels proved that the cause of pain was opioid-induced hyperalgesia. She preferred to have regular dosing throughout the day than spilt into a 12 hourly long-acting preparation. She was discharged by day 8.

She continued to have weekly follow-up within the day therapy structure and as separate appointments with specialist palliative doctors as required. She had remained well on the current dose of opioids until 4 months later when imaging showed further increase in the primary tumour.

DISCUSSION

Opioid-induced hyperalgesia has been recognised clinically but is under-reported. There have been various animal models to try and understand the molecular signalling of opioid hyperalgesia, particularly in comparison to tolerance, withdrawal and addiction. As opioids operate with multisignalling, there are various hypotheses regarding the basis of this phenomenon. It has been postulated that the upregulation of the NMDA receptor antagonist in the dorsal horn neuron may be implicated, hence the success of drugs such as ketamine¹ in its alleviation. The role of μ -receptors, which have been proven to be involved in mechanical allodynia and neuropathic pain, may also have a role.²

Owing to the chronicity in the development of opioid-induced hyperalgesia it is impossible to conduct double-blind trials and therefore most human research has been limited to paradoxical pain study in opioid addicts, patients on methadone maintenance therapy and those receiving acute morphine infusions, such as those during the operative/postoperative period.³ In the latter example high doses of fentanyl and remifentanyl have been implicated in opioid-induced hyperalgesia and controlling these doses has shown a measurable decrease in incidence.⁴ There has been one study by Chu *et al*⁵ using six chronic back pain patients showing a hyperalgesic response after 1 month of oral morphine therapy.

Learning points

- ▶ Opioid-induced hyperalgesia is an important differential in patients with escalating opioid requirements.
- ▶ Diagnosis is clinical and is proven by improvement in overall pain following a decrease/change of opioids.
- ▶ Management requires a tight titration of medication and is often best completed in a clinical setting. Involvement of specialist palliative care/specialist pain clinic is important in diagnosis and management.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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