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Opioid-induced myoclonus and hyperalgesia following a short course of low-dose oral morphine

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Abstract

A 76-year-old man was admitted to hospital with a right-sided fractured neck of femur requiring repair via a cemented hemiarthroplasty. Intraoperatively he received 10 mg of intravenous morphine. Post-operatively he received a short course of low-dose oral opioids and subsequently developed myoclonic jerks and hyperalgesia. The opioids were discontinued and both adverse effects resolved. This case report discusses the concurrent development of myoclonus and hyperalgesia following a low dose of opioids and explores possible management options.

Keywords

Pain perception, opioid, hyperalgesia, myoclonus, adverse effect

Key points

- Opioid therapy may cause myoclonus and hyperalgesia in some patients.
- Both myoclonus and opioid-induced hyperalgesia (OIH) have been previously reported and studied, but have not been reported to occur following a low-dose and mostly oral opioid regime similar to the one utilised in this case.
- No definitive treatment or avoidance measures exist for OIH or myoclonus currently, although opioid dose reduction or opioid switching may be of benefit.

Background

The most common adverse effects of opioid therapy are constipation and nausea. Constipation in particular has a very high incidence, occurring in 40–95% of patients.[1] Other common adverse effects include sedation, vomiting and respiratory depression.[1] Less well-known potential adverse effects include myoclonus, which is defined as sudden, brief, involuntary muscle jerks either irregular or rhythmic,[2] and hyperalgesia, which is defined as an increased sensitivity to pain.[1]

Case presentation

A 76-year-old man presented to the accident and emergency department after a mechanical fall. He had suffered a right intracapsular neck of femur fracture and a simple soft-tissue injury to the right anterior chest wall. There were no visible signs of injury or any other abnormalities to his chest wall, but he had soft tissue tenderness to the right anterior chest wall from approximately the level of the second to the seventh ribs. There was no hyperasthesia on initial presentation. No rib fractures or pneumothorax were identified on chest X-ray. He underwent a right cemented hemiarthroplasty. Intraoperatively, he received 10 mg of intravenous morphine.

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Post-operatively, he complained of ongoing chest pain at the same site that he had injured during his fall. Other significant causes of chest pain were excluded (see investigations below). At this time, he was receiving regular paracetamol as post-operative analgesia. Three days post-operatively, he was commenced on Oramorph solution 5 mg every 6 hours, with additional variable doses of Oramorph 5–10 mg for breakthrough pain. Five days later, he developed brief symmetrical involuntary jerking movements of his arms, legs and neck. The severity of his previously described chest pain increased and he became very sensitive to soft touch at the site of his chest pain. The slightest touch would elicit a severe pain. He did not complain of worsening pain at the site of his hip surgery. By this time, he had received a total of 100 mg of oral morphine in addition to the 10 mg of intravenous morphine he received intraoperatively. After accounting for dose conversion between intravenous and oral morphine, this is equivalent to a total of 130 mg of oral morphine.[3] In the 3 days between receiving 10 mg of intravenous morphine and the commencement of oral morphine, neither myoclonus nor hyperalgesia was observed. These symptoms only developed after oral morphine was commenced.

His past medical history included a cerebral aneurysm, a stroke and carotid artery stenosis. A neurological examination was unremarkable, and the symptoms he had developed did not suggest that he had suffered an intracranial bleed or another stroke.

Investigations

Routine blood tests including full blood count, urea and electrolytes, and liver function tests were all within normal limits. An electrocardiogram (ECG) did not show any new ischaemic or otherwise concerning features. A second chest X-ray, as well as a computed tomography (CT) pulmonary angiogram, and a CT of the head were all normal and aided in the exclusion of other causes of his symptoms.

He was reviewed by a Neurology consultant, who requested a neurological screen (serum copper, ceruloplasmin, anti-basal ganglia antibodies and autoantibodies). These tests were also normal, and a clinical diagnosis of opioid-induced myoclonus and hyperalgesia was made.

Treatment

Seven days after it was originally started, the oral morphine was discontinued. All dyskinetic movements and hyperalgesia resolved within 24 hours. Paracetamol was continued, and pregabalin 75 mg twice daily was commenced. Pain control was achieved, and he was discharged from hospital 5 days later.

Discussion

Myoclonus and hyperalgesia have both been reported to occur following a variety of doses, durations of treatment and routes of administration of various opioids. This case report is different because it describes the concurrent development of both myoclonus and hyperalgesia, following a low-dose, mostly oral, opioid regime. Previously reported cases have involved higher doses of opioids. Furthermore, the development of both of these opioid-related adverse effects at the same time has not been commonly reported in the past.

Opioid-induced myoclonus

There are several reported cases of the development of myoclonus following intrathecal[4–7] and intravenous[8–11] opioid administration. Fewer cases of myoclonus following oral opioid therapy exist in the literature.[12,13] Ito and Liao[12] report one such case in which a 54-year-old man developed myoclonus after 3 weeks of a combination of oral oxycodone and methadone together with buccal fentanyl. Potter et al. found that four out of seven palliative cancer patients in their study, each taking between 150 and 1200 mg of oral morphine per day for an unspecified length of time, developed myoclonus. The doses administered in these cases were higher than the dose administered to the patient under discussion here.

Patel et al.[14] reported the development of myoclonus following a short course of low-dose intravenous opioid treatment. By contrast, no cases of the development of myoclonus following a short course of low-dose oral opioids were identified in this literature search.

Opioid-induced hyperalgesia

Several studies have examined the available evidence regarding opioid-induced hyperalgesia (OIH).[15–20] These publications demonstrate that hyperalgesia can develop after a short course of opioids or after a longer course of low-dose opioids. However, no case reports were found to demonstrate the development of OIH following both a short course length and low dose of opioids, as was demonstrated here.

Concurrent occurrence of opioid-induced myoclonus and hyperalgesia

There are only a few previous reports of the concurrent development of both opioid-induced myoclonus and hyperalgesia. Forero et al.[4] report the development of both these adverse effects at the same time in a patient

receiving long-term high-dose intrathecal hydromorphone. Sjogren et al.[21] describe six cases of the development of one or both adverse effects after moderate to high doses of morphine through a variety of routes of administration. Finally, Sjogren et al.[22] also report the development of both adverse effects in a patient receiving intravenous morphine treatment. However, none of these reports describe a similar opioid regime to the one received by the patient under discussion in this report.

Mechanism of opioid-induced myoclonus and hyperalgesia

Many authors speculate that the neuroexitatory metabolites of opioids, such as morphine and hydromorphone metabolites, may be responsible for opioid-induced myoclonus and hyperalgesia.[23] Several other mechanisms underlying the development of OIH have been proposed, the most commonly discussed being the theory that opioid therapy leads to neuroplastic changes causing an increased sensitivity to excitatory neurotransmitters such as glutamate and N-methyl-D-aspartate (NMDA).[24] It has also been suggested that multiple factors are together responsible and that over time the physiological response to opioids changes, leading to enhanced nociception, rather than analgesia, from opioid exposure.[24] This is consistent with the case under discussion here, where the adverse effects did not occur until several days after opioids were commenced. It is, however, impossible to determine the precise mechanism which may have been responsible in this case.

Management of opioid-induced myoclonus

The management of opioid-induced myoclonus is uncertain. There is some evidence supporting the use of ketamine as a treatment.[4] Two case reports suggest that gabapentin may be effective without a need to reduce the opioid dose.[25] Mercadante[23] also suggests that opioid dose reduction or switching to a different opioid is an option. The same review highlights the possibility that benzodiazepines, dantrolene or baclofen may be useful options if opioid dose reduction is not an option. However, a systematic review of the management of central side effects of morphine[26] concluded that at the time there were insufficient data to make clear recommendations about the management of myoclonus.

Management of opioid-induced hyperalgesia

The possibility of the involvement of NMDA as a mechanism has led to the idea that methadone, an atypical opioid which has antagonistic activity at NMDA-receptors, may be of benefit in avoiding OIH. Indeed, Salpeter et al.[27] have performed a retrospective observational study of palliative care patients and suggest that methadone provides good pain control while avoiding OIH. Chu et al.[15] also highlight six case reports which found that switching opioid-treated patients with suspected OIH to methadone improved their symptoms. Ketamine is another NMDA receptor antagonist, and Chu et al.[15] detail some evidence that it may help prevent OIH, specifically in perioperative patients who receive low-dose ketamine. The cough suppressant dextromethorphan is an NMDA receptor antagonist, and although a number of randomised control trials investigating the use of MorphiDex (a 1:1 mixture of morphine and dextromethorphan)[28] in the treatment of chronic pain have been conducted, there is currently no clear evidence that dextromethorphan might aid in the management of OIH. Prostaglandins are thought to be involved in the modulation of nociceptive processing and can stimulate glutamate release in the spinal cord, and a study by Troster et al.[29] found that the administration of the cyclooxygenase-2 (COX-2) inhibitor parecoxib prior to opioid exposure attenuated remifentanil-induced hyperalgesia.

In summary, many different methods of managing opioid-induced myoclonus and hyperalgesia have been proposed, but there is currently insufficient evidence to point towards the superiority of a single method.

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