

Case Discussion: A Case of Hypercalcaemia Mimicking Opioid Toxicity

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Abstract

Here we present a case of hypercalcaemia mimicking opioid toxicity. This is a 50 year old lady with a neuroendocrine tumour who presented with worsening back pain, thoracic wall pain, constipation, fatigue, confusion and nausea. Her regular morphine dose had recently been increased and she was initially admitted to hospice for management of these symptoms, which were believed to be due to opioid toxicity. However, investigations showed hypercalcaemia and she was treated adequately for this. Her symptoms were well controlled, although she continued to deteriorate due to the underlying malignancy and she remained on opioids for her end-of-life pain management. Hypercalcaemia and opioid toxicity have several overlapping symptoms, including fatigue, confusion, nausea and vomiting, constipation and abdominal pain. However there are specific signs and symptoms to help distinguish the two. Specifically, opioid toxicity can cause respiratory depression, miosis and myoclonic jerks while hypercalcaemia can cause bone pain, renal colic, arrhythmias, polyuria and polydipsia. Therefore attention should be paid to these specific features on assessment of patients and blood tests should be done if there is any uncertainty.

Keywords: Hypercalcaemia; Nausea; Opioid toxicity; Morphine; Curative treatment

Introduction

Both hypercalcaemia and opioid toxicity are commonly observed in palliative medicine. Because they can result in many overlapping symptoms, the diagnosis is not always immediately obvious, especially when laboratory investigations and blood tests are not done as routinely in palliative settings compared to acute hospital admissions. It is no surprise that diagnosing the symptoms of hypercalcaemia as opioid toxicity would lead not only to delay in treatment, but also poor management of pain due to inappropriate reduction in opioid doses. Here, we present a case study of hypercalcaemia mimicking opioid toxicity in a palliative patient, and discuss how to distinguish the two.

Case Description

This was a 50 year-old lady with a diagnosis of a neuroendocrine rectal tumour made two years ago with widespread metastatic disease in the bones and liver. She was not fit for further active or curative treatment, and her prognosis was poor. Her main symptoms had been ongoing rib pain, thoracic back pain and intermittent nausea. The pain had been present for several weeks but acutely worsened over the last few days. She was referred by the community nurses for a medical review due to this increase in pain. She had been taking modified-release morphine 10 mg BD and ibuprofen 400 mg TDS, with approximately 5 breakthrough doses of immediate-release morphine a day, all of which were partially effective in alleviating her pain, albeit only temporarily. She had also been increasingly constipated but responsive to laxatives.

On examination, she appeared uncomfortable and in pain. She was orientated in time, place, and person, with no signs of confusion identified. No myoclonic jerks were observed. Her pupils were

approximately 3 mm in diameter, equal and reactive to light. No focal neurology was noted. She had a respiratory rate of 16 and a regular heart rate of 90. She was tender over the ribs across the anterior chest and in the thoracic spine. The rest of the examination was unremarkable.

Her modified-release morphine was increased to 20 mg BD and the breakthrough doses adjusted appropriately, with the plan to further increase the opioid doses over the next few days.

She was admitted to the hospice three days later due to increased drowsiness, intermittent confusion, worsening constipation and nausea. In the context of recently increased morphine doses, these worsening symptoms were initially thought to be due to opioid toxicity. Calcium studies were done, which revealed corrected calcium of 3.55 mmol/L. Her previous calcium from a month ago had been normal.

She did not want to be admitted to hospital, so she was managed in the hospice for hypercalcaemia with intravenous fluids and zoledronic acid infusion. The morphine doses were titrated up appropriately for the chest and back pains. Because the team had been quick to act on the hypercalcaemia, her symptoms of pain, constipation, nausea and confusion gradually improved and her corrected serum calcium started to normalize after a week.

Unfortunately, while her symptoms were well controlled, she continued to generally deteriorate, becoming increasingly fatigued due to the progression of the cancer. She died peacefully after another week.

Discussion

In patients with metastatic bone disease, clinicians are often vigilant about the signs and symptoms of hypercalcaemia. However, in this scenario, the recent increase in morphine doses made opioid toxicity a much more likely cause of the worsening symptoms, like nausea,

constipation, tiredness and confusion. It was only with the laboratory results showing hypercalcaemia that the true culprit was identified. Here, we shall discuss the signs and symptoms of hypercalcaemia, opioid toxicity, and the specific features that help distinguish the two.

Hypercalcaemia

Hypercalcaemia is most commonly caused by primary hyperparathyroidism and malignancy-associated hypercalcaemia, the latter of which is prevalent in palliative medicine and could account for about 38% of acute presentations of hypercalcaemia [1]. Additionally, hypercalcaemia has been reported to present in up to 10-30% of cancer patients at some point in their illness [2]. The pathogenesis of malignancy-associated hypercalcaemia has been shown to be due to (1) the production of parathyroid hormone-related peptide, which can bind to parathyroid hormone receptors and thus mimic its function, (2) increased bone resorption in the cases of metastatic bone disease, and (3) ectopic hormone secretions [3].

Symptoms of hypercalcaemia are protean, encompassing a variety of gastrointestinal, renal, neuromuscular and cardiovascular manifestations. The severity of the symptoms ranges from asymptomatic to life-threatening and may vary depending on the chronicity of the problem and the degree of increase in serum concentration of calcium. Common symptoms including bone pain, drowsiness, impaired cognition, muscle weakness, nausea and vomiting, constipation, renal colic due to renal stones, polyuria and polydipsia, and arrhythmias.

The National Institute for Health and Care Excellence (NICE) recommends the administration of intravenous fluids and bisphosphonates as the treatment for hypercalcaemia in known malignancies [4]. Other treatments include the use of calcitonin, denosumab, calcimimetics and dialysis.

Opioid toxicity

Strong opioids are commonly used in the management of pain in advanced, life-limiting cancers. Opioids bind to and activate the mu, kappa and delta opioid receptors which are widespread in the central and peripheral nervous systems as well as the gastrointestinal system. Classically, the supraspinal and spinal mu opioid receptors are believed to be largely responsible for the analgesic effects of exogenous opioids like morphine, although the evidence is constantly evolving [5]. However, the downstream actions of these receptors are not only nociceptive in nature, and high doses of opioids and their metabolites can result in side effects that are collectively referred to as opioid toxicity.

Common signs and symptoms of opioid toxicity include respiratory depression, myoclonic jerks, miosis, hallucinations, drowsiness and confusion. These features are not always consistently present, with the most specific sign for opioid toxicity being respiratory depression, defined as a respiratory rate of less than 8-12 breaths per minute [6].

When opioid toxicity is suspected, the management depends on the severity of the symptoms. In palliative care, this would include titrating down the dose of opioids or switching to a different opioid [7]. If signs of respiratory depression are identified, then naloxone 100-200 micrograms is given in boluses while assessing the response.

Distinguishing features

The common and distinguishing features of opioid toxicity and hypercalcaemia are summarised in the Table 1:

| Common features | |
|---------------------------------|-------------------------|
| Fatigue and drowsiness | |
| Confusion | |
| Nausea and vomiting | |
| Constipation and abdominal pain | |
| Opioid toxicity | Hypercalcaemia |
| Respiratory depression | Polyuria and polydipsia |
| Miosis | Bone pain |
| Myoclonus | Renal colic |
| | Cardiac arrhythmias |

Table 1: Common and distinguishing features of opioid toxicity and hypercalcaemia.

In the case described above, the patient presented with worsening drowsiness, nausea and intermittent confusion, all of which are common between opioid toxicity and hypercalcaemia. However, in retrospect, we can see that even prior to admission; she had several features that were more suggestive of the latter. For example, she had a normal respiratory rate, normal pupils and no myoclonic jerks, pointing away from opioid toxicity; she had also been complaining of worsening pain in the ribs and thoracic spine, consistent with bone pain from hypercalcaemia.

Conclusion

As discussed above, hypercalcaemia in malignancy can be very common, and as such it is important for clinicians to have a high index of suspicion for it when assessing patients with cancer. However, there are several overlapping signs and symptoms of hypercalcaemia and opioid toxicity which are not always immediately distinguishable. Often, the clinical history, for example, a recent increase in opioid use will point towards one or the other, but as illustrated in this case study, that is not always the case. As such, it is important to be aware of their respective specific features, and if there is any diagnostic uncertainty between the two, calcium studies should be done as soon as possible to guide the appropriate management of the patient.

Declarations

The authors of this paper have no conflicts of interest to declare.

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