CASE REPORT

Cautious use and optimal dose of morphine for relieving malignant pain in a complex patient with multiple comorbidities

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Accepted 1 December 2016

SUMMARY

Oral morphine remains the drug of choice for the management of severe pain due to cancer as per WHO ladder of analgesia. Providing adequate pain relief in palliative care settings for pain due to cancer is challenging. Options become limited in cases of associated systemic comorbidities such as renal dysfunction, hypoproteinaemia, anaemia. Patients with renal dysfunction and other comorbidities may develop drug overdose due to abnormal pharmacokinetics. Renal dysfunction affects the pharmacokinetics of morphine by altering its absorption, metabolism and clearance. Plasma albumin also influences drug availability, its plasma distribution and thus available free morphine for its clinical effect. Morphine should be used cautiously for the treatment of pain in patients with renal failure, hypoproteinaemia, hyperbilirubinaemia and anaemia. In such patients, alternate opiates like fentanyl, hydromorphone, or oxycodone may be used as these drugs are not significantly excreted by the kidneys.

BACKGROUND

Most palliative care physicians are familiar with the use of morphine in patients suffering from pain due to cancer. It provides effective analgesia; therefore, it is the drug of choice for management of severe pain due to cancer. However, it may also cause nausea, vomiting, constipation, and rarely respiratory depression. Morphine is widely available and is inexpensive. Owing to these reasons, morphine is preferred over other opioid drugs. We describe a case of morphine overdose in a patient with cancer having multiple comorbidities like hepatorenal dysfunction, anaemia and hypoproteinaemia.

CASE PRESENTATION

A 66-year-old woman was seen at our outpatient clinic. Her body mass index was 25 kg/m². She reported severe pain in lower abdomen and over the lumbar region. She had 1 year history of transitional cell carcinoma (TCC) of urinary bladder. The tumour was excised and an ileal conduit for urinary diversion was formed. She also underwent right nephrectomy for TCC in the right kidney 3 years ago. During that time, the patient's liver and kidney function was normal. Five months prior to this admission, she developed urinary tract infection, which progressed to pyelonephritis and mild hydronephrosis. Her condition was medically managed with antibiotics and supportive care. This last event exposed her to a series of recurrent

urinary tract infections (thrice during the last 4 months) and gradually deteriorating renal functions. It was during this period that she started getting pain in the abdomen. Initially her pain was controlled with non-steroidal anti-inflammatory drugs which were later stopped in the wake of decreasing creatinine clearance. She was prescribed oral tramadol to which she developed allergic reaction and her pain was inadequately relieved. At this juncture, the patient was referred to palliative care. In view of the severe pain in the lower abdomen (NRS (numerical rating scale of pain) of 7 of 10), oral morphine (5 mg) was initiated every 4 hourly and 5 mg for breakthrough pain as a rescue analgesic. Two days later, the patient was noted to be drowsy and difficult to arouse, not responding to verbal stimuli. Her respiratory rate was 7–8 bpm although she was haemodynamically stable. Her neurological assessment was inconclusive except for the pinpoint pupils. Her morphine intake was as per schedule. A diagnosis of morphine overdose was made. She was admitted to palliative care ward. Her heart rate was 75 bpm, blood pressure was 110/70 mm Hg, respiratory rate was 8/min and oxygen saturation was 92% on room air. We kept emergency drugs, including naloxone, near bedside in case they were required for emergency use.

INVESTIGATIONS

Blood samples were collected for testing kidney and liver functions. Her serum creatinine was 3.8 mg/dL, total serum bilirubin was 3.2 mg/dL and blood sugar was 110 mg/dL. She had a low level of plasma albumin (2.1 g/dL). The patient was severely anaemic (Hb 6.5 g/dL). Her next dose of morphine was withheld.

TREATMENT

On the day after treatment was initiated (or morphine withheld), she was transfused with 3 units of packed red blood cells and 4 units of fresh frozen plasma over the next 12 hours. She was infused with 100 mL human albumin 20% once a day for 3 days. During this period the patient's vital fluid input–output, respiratory rate and neurological status were monitored. The next day, the patient became conscious and was following verbal commands. She was started on intravenous fentanyl 10 µg/hour and was titrated over next 4 hours with NRS. She was also administered oral paracetamol 500 mg every 8 hourly. She had optimal pain relief (NRS <4) on fentanyl infusion of 25 µg/hour.

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To cite: Kumar V, Garg R, Gupta N, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217174

Subsequently, a fentanyl transdermal patch of 25 µg/hour was applied and fentanyl infusion was tapered over the next 8 hours but paracetamol 500 mg every 8 hours was continued.

OUTCOME AND FOLLOW-UP

She was prescribed fentanyl transdermal patch of 25 µg/hour and paracetamol 500 mg every 8 hours. The patient reported satisfactory pain relief on the follow-up visit.

DISCUSSION

The management of severe pain in patients with advanced cancer is challenging. Although opioids remain the mainstay of management, its metabolism needs to be understood. We briefly describe the morphine metabolism for better understanding of pain management in patients with associated comorbidities that could affect pharmacokinetics and pharmacodynamics of morphine.

Ninety per cent of morphine is metabolised by the liver, with a significant first pass effect on oral administration. The remaining 10% of morphine is excreted in urine. Approximately 70% of morphine undergoes conjugation with glucuronides. There are two major glucuronides forms—morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G as compared to M3G is pharmacologically more active and potent than morphine. It has intense analgesic effect in addition to side effects of nausea and vomiting, sedation and the risk of respiratory depression. Myoclonus and allodynia may occur as side effects of M3G when large doses of systemic morphine are administered. These glucuronides are excreted by the renal tubules, and they accumulate in the presence of renal failure and cause morphine toxicity.^{1 2}

Elderly patients have reduced volume of distribution and receptors for drug binding. They also have decreased clearance of drugs due to hepatic and renal insufficiency.³ It may prolong the duration of action of administered drug and potentiates their side effects.⁴

In TCC, neoadjuvant chemotherapy (cisplatin) is usually administered as a part of chemotherapeutic management. This drug may also cause renal dysfunction. Urinary diversion in the form of ileal conduit is made after radical cystectomy. It has been reported that glomerular filtration rate decreases about 15–25% after urinary diversion. It also affects drug kinetics as 10% of morphine secreted in urine may get reabsorbed, thereby increase the serum level of morphine may cause overdose.⁵

In liver dysfunction, morphine clearance is reduced and oral bioavailability is increased. This increases the risk of drug accumulation in the body.⁶ Also liver dysfunction could affect the protein levels of the body if its synthetic function is deranged. Our patient was suffering from severe anaemia with an Hb of 6.5 gm/dL. Low haemoglobin may be associated with hypoproteinaemia and our patient was also suffering from serum hypoalbuminaemia. Hypoalbuminaemia due to liver or renal dysfunction raises the unbound fraction of morphine that crosses blood–brain barrier. Bilirubin competitively binds with albumin and thereby raises the free fraction of morphine.^{7 8} Morphine binding with albumin is severely diminished in

hyperbilirubinaemia. So, patients having hepato-renal dysfunction with low albumin are very sensitive to usual doses of morphine due to increased free portion of morphine.⁶

To conclude, morphine should be used cautiously for pain management due to cancer in medically frail patients having renal failure, hypoproteinaemia, hyperbilirubinaemia and anaemia. In such patients, alternate opiates such as fentanyl, hydromorphone and oxycodone may be used as these drugs are not significantly excreted by the kidneys. Kidney and liver functions should be monitored whenever clinically indicated. In case of deranged kidney and/or liver functions opioid, the drugs dosages should be adjusted to meet the needs of individual patients and ensure their safety.

Learning points

- ▶ Morphine should be used cautiously for the treatment of pain in patients with renal failure, hypoproteinaemia, hyperbilirubinaemia and anaemia.
- ▶ Alternate opiates which are not significantly excreted by the kidneys like fentanyl, hydromorphone and oxycodone may be used in renal dysfunction patients.
- ▶ Kidney function test and proteins levels should be monitored regularly.
- ▶ Drugs dosages should be reviewed and adjusted as per derangement.

Contributors VK involved in the conduct and follow-up of the care. VK and RG planned the study, collected case-related data, involved in literature search and wrote the manuscript. RG, NG, SJB were involved in conduct and follow-up of care. All approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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