**The analgesic benefit of treating hypomagnesaemia**

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**Abstract**

The role of magnesium as an analgesic in patients is unclear. Hypomagnesaemia is a common electrolyte abnormality, in the chronic state symptoms are insidious and often non-specific. It is often undiagnosed and thus untreated. There is evidence from animal studies that magnesium is involved in pain control including an animal model of hyperalgesia induced by hypomagnesaemia. We report two cases of patients admitted for pain control which improved when hypomagnesaemia was treated. Each case had metastatic cancer. Both were found on admission to have asymptomatic hypomagnesaemia and were treated with IV magnesium. Treatment for hypomagnesaemia resulted in an improvement in pain control such that analgesia was decreased. The incidence of hypomagnesaemia in palliative patients is unknown although it is thought to be common. These cases suggest that treating hypomagnesaemia may improve pain control.

**Background**

Magnesium is an essential ion. It acts as a cofactor in many enzymatic reactions and has a crucial role in the electrical properties of membranes. Hypomagnesaemia in the general population is estimated to be between 2.5 and 15%. It is much higher (10-65%) in patients being treated in hospices, hospitals and in critical care units (1). Approximately half of the total body magnesium is intracellular, the other half is in bone. Less than 1% is present in blood serum. Hypomagnesaemia is often under recognised because serum magnesium levels are an insensitive guide to total body stores. The best test for detecting magnesium deficiency is the magnesium loading test (2).

Hypomagnesaemia can produce numerous symptoms; fatigue, pain, cramps, convulsions, hallucinations, torsades de pointes. In chronic deficiency, symptoms are insidious in onset, less severe and non-specific (2). The most frequent causes in patients with advanced disease are the use of cisplatin, cetuximab and proton pump inhibitors (1).

It is thought that magnesium can impact both inflammatory and neuropathic pains through a number of mechanisms. In the spinal dorsal horn magnesium can: decrease N-methyl-D-aspartic acid (NMDA) receptor activity by blocking the receptor-coupled calcium channel, allosterically antagonising action on the receptor; reduce spinal cord NMDA receptor phosphorylation; decrease the production of substance P thus diminishing its pro-inflammatory action; potentiate the action of morphine in the presynaptic area of the dorsal horn; and reduce the activity of other presynaptic or postsynaptic calcium channels. The peripheral actions of magnesium include a reduction of thromboxane A2 (pro-inflammatory) and the synthesis of certain cytokines e.g. TNF alpha (3). In animal studies, magnesium deficiency results in a pro-inflammatory state including hyperalgesia (4). This is thought to relate to magnesium acting as a natural ‘calcium antagonist’. With decreasing magnesium levels, intracellular calcium levels increase, activating processes that contribute to inflammation (2).

Research for magnesium administration on pain is conflicting. Some authors have reported the lack of any effect of magnesium in pain; other authors have shown that magnesium can influence pain intensity and consequently the requirement for analgesics or anaesthetic drugs (3). This was recently reviewed by Centeno & López Saca (1). None of the studies looked at patients with hypomagnesaemia.

**Case 1**

**Case presentation**

73-year-old male admitted to optimize his analgesia and for consideration of ketamine infusion. He had Non-Small Cell Lung Cancer with bone metastases and presented with increasing left sub-scapular pain secondary to a new scapular metastasis.

**Case management**

On admission, his analgesic medications included; oxycodone MR 50mg bd, pregabalin 100mg bd, paracetamol 1g PRN qds, naproxen 500mg bd and oxycodone IR 10mg PRN. A 5% lidocaine plaster was added on the day of admission to provide local analgesia.

Routine bloods taken on day 1 showed: Corrected Calcium 1.94mmol/L and Magnesium 0.19mmol/L. Other biochemistry was unremarkable. The patient was asymptomatic from a hypomagnesaemia perspective and was treated with 20mmols magnesium IV on day 2 of the admission. Repeat magnesium level was 0.86mmol/L on day 4.

From days 1 to 3 he required three breakthrough doses of oxycodone IR 20mg per day. Therefore, his oxycodone MR was increased on day 3 to 70mg bd. This was subsequently reduced to 60mg the following day due to nausea. On day 5 he became clinically opioid toxic with no responsible change in his blood biochemistry. His oxycodone MR was decreased from 60 to 40mg bd. 24 hours later there was no evidence of opioid toxicity and his pain was well controlled. He required only two doses of oxycodone IR 10mg between days 7 and 12.

On day 12 he complained of pain relapse. A repeat magnesium was 0.53mmol/L and he was given another IV infusion of 20mmols magnesium. His pain resolved with no change to his analgesia.

**Case outcome**

He was discharged home on day 14 with a reduced dose of oxycodone 40mg bd and oral magnesium supplements. After discharge, he had no further reports of pain. He subsequently died 8 days later.

**Case 2**

**Case Presentation**

64-year-old male admitted for pain control. He had large cell neuroendocrine cancer with multiple pulmonary, vertebral and chest wall metastases. He had previously received radiotherapy to his spine (T7-9) and sternum for pain control. He had multiple admissions to the hospice over the previous number of months for pain control.

**Case Management**

His analgesia on admission included; oxycodone MR 130mg bd, pregabalin 300mg bd, paracetamol 1g qds and a lidocaine 5% plaster. Prior opioid toxicity prevented uptitration of his oxycodone, therefore he was rotated to hydromorphone MR 20mg bd on admission. Hydromorphone IR 6.5mg was used prn for breakthrough pain. Between days 1 and 5, prn hydromorphone was used on average 3 times per day for breakthrough pain. On day 5 hydromorphone MR was increased to 28mg bd and routine bloods showed a magnesium of 0.48mmol/L with no other biochemical abnormalities.

On day 6, this was treated with 20mmol magnesium IV. Between days 7 and 9 his pain was well controlled but he developed intolerable drowsiness (without other signs of opioid toxicity). During this time, his hydromorphone MR dose was reduced to 10mg bd and his pain remained well controlled.

Between days 10 and 13 the patient’s pain remained well controlled with 1 prn dose of hydromorphone IR 2.6mg per day on average. However, the patient requested a rotation back to oxycodone due to concerns about recurrence of his drowsiness. He was therefore recommenced on oxycodone MR 80mg bd.

**Case outcome**

The patient was successfully maintained on 80mg oxycodone MR bd with good pain control; a significant decrease compared to his admission dosage. He remained in the hospice for a further 4 weeks due to other psychosocial interventions, and was discharged thereafter.

**Conclusion**

Some patients present with pain which is often difficult to treat. Despite many animal studies that have shown magnesium to have numerous sites of action on pain mechanisms, human trials have not consistently demonstrated the efficacy of magnesium as an analgesic.

These two cases demonstrate that the treatment of hypomagnesaemia may improve pain in patients with advanced cancer. Hypomagnesaemia is often under recognised because serum magnesium levels are an insensitive guide to total body stores. These cases suggest that magnesium levels should be assessed in patients with advanced cancer with complex pain or inexplicable neurological symptoms. Further research is needed to determine the effect of treating hypomagnesaemia on pain.

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**Declarations**

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SC and DM contributed to the writing of the paper.

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**Declaration of competing interests**

The Authors declare that there are no competing interests.

**Research ethics and patient consent**

Consent for use of each patient details was obtained from the next of kin as each patient had subsequently died.

**Data management and sharing**

No additional data available