Original Article

The Safety and Efficacy of a Single Dose (500 mg or 1 g) of Intravenous Magnesium Sulfate in Neuropathic Pain Poorly Responsive to Strong Opioid Analgesics in Patients with Cancer

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Abstract
Neuropathic pain may respond poorly to morphine and is often difficult to relieve. Recent attention has been drawn to the role of the N-*methyl-*D*-aspartate (NMDA) receptor in the potentiation of neuropathic pain. Magnesium is known to block the NMDA receptor. It reduces the neuropathic pain response in animals, and attenuates postoperative pain and migraine in humans. We have examined the safety, tolerability, and efficacy of two intravenous doses of magnesium sulfate in 12 patients with neuropathic pain due to malignant infiltration of the brachial or lumbosacral plexus. The first six patients received 500 mg, the remainder 1 g. Apart from a mild feeling of warmth at the time of the injection, both doses were well tolerated. After receiving 500 mg, three patients experienced complete pain relief and two experienced partial pain relief for up to 4 hours duration; pain was unchanged in one patient. After receiving 1 g, one patient experienced complete relief and four experienced partial pain relief of similar duration; pain was unchanged in one patient. Intravenous magnesium sulfate in these doses appears to be safe and well tolerated. A useful analgesic effect may be obtained in some patients and further evaluation is warranted.* J Pain Symptom Manage 2000;19:35–39. *© U.S. Cancer Pain Relief Committee, 2000.*

Key Words
Magnesium sulfate, neuropathic pain, cancer

Introduction

Neuropathic pain occurs in up to 34% of patients with cancer[1] and is difficult to treat because it responds inconsistently to opioid analgesics.[2,3] The use of other pharmacological approaches, such as anticonvulsants, tricyclic antidepressants, and oral local anesthetics can be limited by inconsistent benefit or adverse effects.[4] A variety of other therapeutic strategies, such as spinal analgesia (epidural or intrathecal) may need to be considered. More recently, ketamine has been used with some benefit in neuropathic pain,[5] possibly by acting as an antagonist at the *N*-methyl-D-aspartate (NMDA) receptor. This receptor appears to play an important

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role in the potentiation of pain.[6] Unfortunately, the use of ketamine can be limited by unpleasant psychomimetic side effects.[5]

Magnesium also acts as an NMDA antagonist,[7] suppressing neuropathic pain response in animals[8] and improving migraine[9] and postoperative pain in humans when given intravenously.[10] A bolus of magnesium chloride (0.16 mmol/kg) followed by an infusion (0.16 mmol/kg/hour) improved pain in some but not all patients with chronic neuropathic pain of various etiologies.[11]

We felt that the analgesic effect of magnesium warranted further evaluation in patients with neuropathic pain due to cancer. As the safety and efficacy of magnesium had not been examined in this group of patients, we first carried out this pilot study.

Methods

Subjects

Twelve patients (7 male), mean (SD, range) age 63 (9, 45–74), with cancer were recruited from a specialist palliative care unit. Mean (SD, range) weight and Eastern Cooperative Oncology Group (ECOG) performance status were 66 kg (12, 36–93) and 1.6 (0.5, 1–2), respectively. All had neuropathic pain due to cancer infiltrating the brachial (5) or lumbosacral (7) plexus. This diagnosis was confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scan. Pain persisted despite the use of strong opioids together with anticonvulsants and tricyclic antidepressants in combination (6), anticonvulsants alone (4), or tricyclic antidepressants alone (2). The opioid dose had been titrated until further dose increments produced no additional benefit. The mean (SD, range) daily morphine equivalent dose was 200 mg (125, 20–400). Pain was at least of moderate intensity as rated by the patient on a 5-point scale (Table 1). Patients were excluded if they had hypermagnesemia, hypercalcemia, any degree of heart block, renal impairment (blood urea $>$ 12 mmol/L and creatinine $>$ 150 μmol/L), or were taking digoxin. Patients in whom psychological distress was thought to be a major contributing factor to their pain experience were also excluded. All patients gave written informed consent and the study was approved by the Nottingham City Hospital Ethics Committee.

Table 1
Pain Intensity and Pain Relief Scales

Pain Intensity Scale	
At present my pain is best described as:	
Very severe pain	4
Severe pain	3
Moderate pain	2
Mild pain	1
No pain	0
Pain Relief Scale	
My pain has:	
Been completely relieved	4
Been almost completely relieved	3
Eased moderately	2
Eased only slightly	1
No change	0
Become slightly worse	−1
Become moderately worse	−2
Become almost maximal	−3
Become maximal	−4

Test Procedure

All subjects were inpatients. The study was not undertaken within 1 hour of an immediate-release preparation or within 4 hours of an extended-release preparation of a strong opioid. With the patient recumbent, an 18-gauge intravenous (IV) catheter was inserted into an antecubital vein to give the injection and to allow blood sampling. One ml or 2 ml of 50% w/v magnesium sulfate BP (Pharmacy Manufacturing Unit, Torbay Hospital, Torquay, UK) was given intravenously over 5 or 10 minutes (500 mg or 1 g, respectively). Assessment of pain, heart rate, and systolic and diastolic blood pressure (mean of two readings using an Accoson mercurial sphygmomanometer, Accoson, UK) were made prior to the injection of magnesium sulfate and then every 15 minutes for the first hour, then after 4 and 24 hours. Total serum magnesium was measured before the injection, then at 15, 30, 60 minutes and 24 hours using an Olympus AU 800 analyzer employing the xylidylblue method[12] (normal range for our laboratory 0.7–1.0 mmol L^{-1}). Patients remained on their bed for the first hour and were asked to report any adverse effects. After the first six patients tolerated magnesium sulfate 500 mg without problems, a further six patients received 1 g.

Results

Safety

Following either dose of magnesium sulfate, all patients experienced a feeling of warmth.

This was more noticeable following 1 g. It was a mild sensation felt in the upper chest and perineum lasting for 2–3 minutes and did not cause undue distress. There were no other adverse effects. Changes in heart rate, and in systolic and diastolic blood pressure, were minimal and not clinically apparent. Following the 500-mg dose, mean (range) total serum magnesium increased from 0.8 (0.7–0.9) mmol/L to a peak of 0.9 (0.8–1.1) mmol/L after 15 minutes. This was unchanged after 60 minutes but had returned to baseline after 24 hours. After 1 g, mean (range) total serum magnesium increased from 0.7 (0.6–0.8) mmol/L to a peak of 1.0 (0.8–1.1) mmol/L after 15 minutes. This level had fallen by 60 minutes but at 24 hours remained elevated compared to baseline 0.8 (0.7–0.9).

Efficacy

500 mg: Mean pain severity and pain relief scores improved following the 500-mg dose (Figure 1). Pain was completely relieved in three, partially relieved in two, and unchanged in one patient. Improvement began after 15 minutes and maximum benefit appeared between 45 and 60 minutes. Useful analgesia was maintained for up to 4 hours. At 4 hours, all patients reported that pain was returning and one patient reported that pain had returned to baseline.

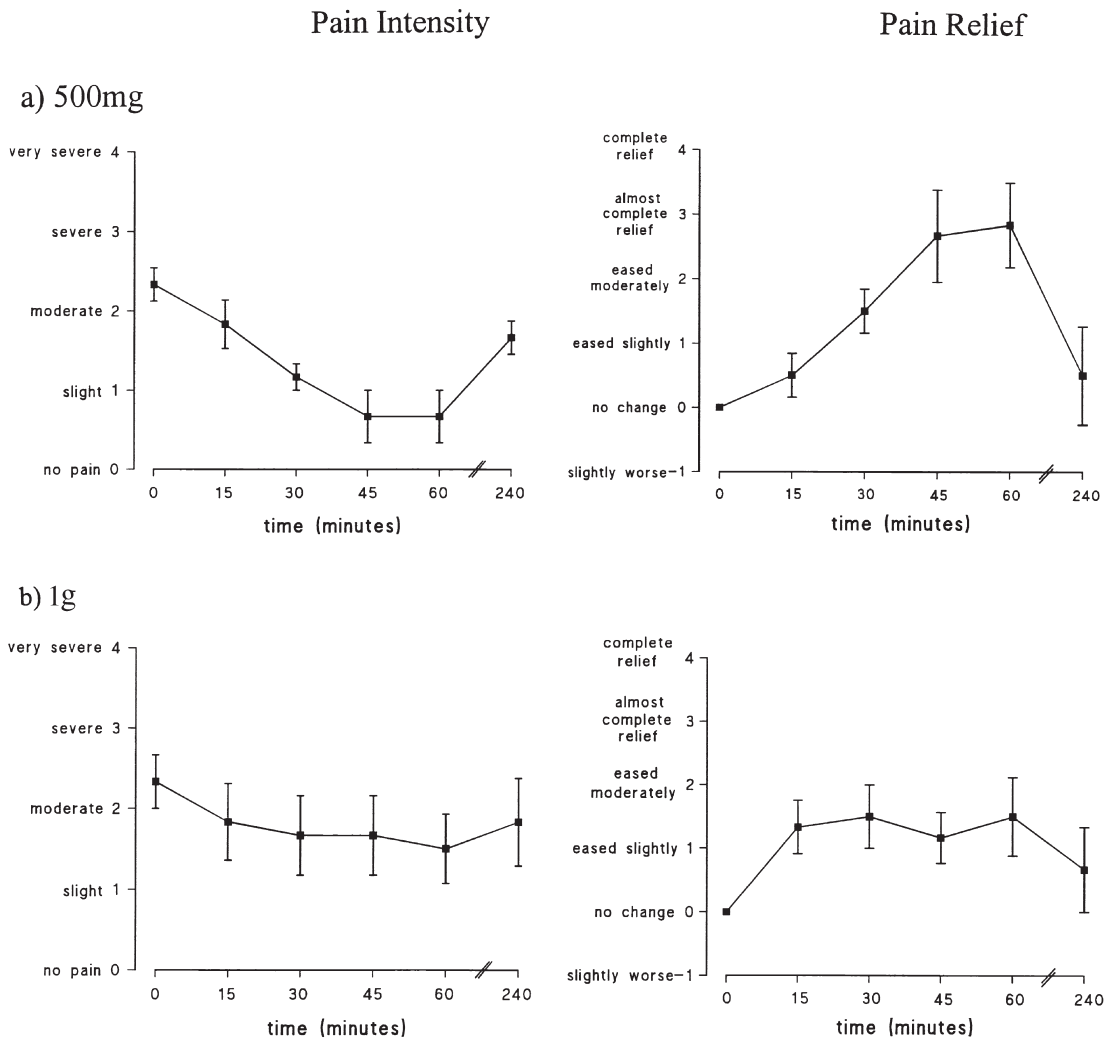

Fig. 1. Mean (SEM) pain intensity and pain relief scores for 500 mg and 1 g of intravenous magnesium sulfate.

1 g: Mean pain severity and pain relief scores improved following the 1-g dose (Figure 1). Pain was completely relieved in one, partially relieved in four, and unchanged in one patient. Improvement began after 15 minutes and maximum benefit was noted at 60 minutes. Useful analgesia was maintained for up to 4 hours. At 4 hours, two patients still reported an analgesic effect, two reported that pain was beginning to return, and one patient stated that the pain had returned to baseline.

There was no correlation between serum magnesium and clinical response.

Discussion

In previous studies, magnesium given either as an IV bolus of 1 g, or an IV bolus of 3 g followed by an infusion of 10 g over 20 hours, has been reported to have a useful analgesic effect in migraine and postoperative pain.[9,10] It was well-tolerated apart from a flushed feeling experienced by all patients, and light-headedness for a few minutes when sitting up in 12 of 40 patients.[9] This benefit was thought to result from its actions as a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, which is believed to have an important role in the transmission of pain.[6]

We wished to examine the use of magnesium in patients with neuropathic pain due to cancer. In this pilot study, we were particularly concerned with the tolerability and safety of magnesium sulfate given IV to patients with advanced cancer. We purposely selected doses that were smaller than those used in previous studies in otherwise "healthy" subjects[11] and generally lower than those used for the treatment of acute myocardial infarction and preeclampsia.

Apart from a mild feeling of warmth, both the 500-mg and 1-g doses were well tolerated and the mean increase in total serum magnesium to 0.9 and 1.0 mmol/L, respectively, is well below the level of 2.0 mmol/L at which toxicity has been reported.[13] None of the changes in heart rate, systolic or diastolic blood pressure were clinically apparent, although patients were asked to remain recumbent for 1 hour after the injection.

For each dose, a similar number of patients reported some degree of analgesia. There was no obvious dose effect although the study was not designed to look at this. Similarly, the design does not allow us to rule out a placebo effect, which is reported to be as high as 60% in patients with neuropathic pain.[14] The lack of correlation between initial levels of serum magnesium and analgesic response is not surprising given our small sample size.

In summary, we have found that IV magnesium sulfate in bolus doses of 500 mg and 1 g appears safe, well tolerated, and potentially effective in patients with neuropathic pain due to cancer. Controlled trials of this treatment are warranted. The relationship between degree and duration of benefit with dose, frequency, route of administration, and magnesium status should be examined.

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References

1. Zech DFJ, Grond S, Lynch J, Hertel D, Lehman KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain 1995;63:65–76.

2. Cherny NI, Thaler HT, Freidlander-Klar C, Lapin J, Foley KM, Houd R, Portenoy RK. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single dose studies. Neurology 1994;44:857–861.

3. Jaded AR, Carroll D, Glynn CJ, Moore RA, McQuay HJ. Morphine responsiveness of chronic pain: double blind randomised crossover study with patient controlled analgesia. Lancet 1992;339:1367–1371.

4. Martin LA, Hagen NA. Neuropathic pain in cancer patients: mechanisms, syndromes and clinical controversies. J Pain Symptom Manage 1997;14:99–117.

5. Luczak J, Dickenson AH, Kotlinska-Lemieszek A. The role of ketamine, an NMDA receptor antagonist, in the management of pain. Progress Palliat Care 1995;3:127–134.

6. Dickenson AH. A cure for wind up: NMDA receptor antagonists as potential analgesics. Trends Pharmacol Sci 1990;11:307–309.

7. Evans RH, Francis AA, Watkins JC. Mg^{2+} like selective antagonism of excitatory amino acid induced responses by alpha-epsilon-diaminopimelic acid, d-alpha-aminoadipate and HA-996 in isolated spinal cord of frog and immature rat. Brain Res 1978;148:536–542.

8. Xiao WH, Bennett GJ. Magnesium suppresses neuropathic pain responses in rats via a spinal site of action. Brain Res 1994;666:168–172.

9. Mauskop A, Altura BT, Cracco RQ, Altura BM. Intravenous magnesium sulfate relieves migraine attacks in patients with low serum ionised magnesium levels: a pilot study. Clin Sci 1995;89:633–636.

10. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996;84:340–347.

11. Felsby S, Neilson J, Arendt-Neilson L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. Pain 1995;64:283–291.

12. Mann CK, Yoe JH. Spectrophotometric determination of magnesium with 1-azo-2-Hydroxy-3-(2,4 Dimethylcarboxanilido)-naphthalene-1-(2-Hydroxybenzene). Anal Chim Acta 1957;16:155–160.

13. Durlach J, Durlach V, Bac P, Bar M, Guiet-Bara A. Magnesium and therapeutics. Magnes Res 1994;7: 312–328.

14. Verdugo RJ, Ochoa JL. Placebo response in chronic causalgiform, "neuropathic" pain patients: study and review. Pain Rev 1994;1:33–46.