Efficacy of intravenous magnesium in neuropathic pain

S. Brill[1], P. M. Sedgwick[2], W. Hamann[1 3] and P. P. di Vadi[1]*

[1]Department of Anaesthetics and Pain Management, University Hospital Lewisham, Lewisham High Street, London SE13 6LH, UK. [2]Department of Public Health Sciences, St George's Hospital Medical School, London SW17 ORE, UK. [3]GKT School of Medicine, Pain Management Unit, Guy's and St Thomas' Hospital, London SE1 9RT, UK

*Corresponding author

Background. Postherpetic neuralgia is a complication of acute herpes zoster characterized by severe pain and paraesthesia in the skin area affected by the initial infection. There is evidence that the *N*-methyl-D-aspartate receptor is involved in the development of hypersensitivity states and it is known that magnesium blocks the *N*-methyl-D-aspartate receptor.

Method. A double-blind, placebo-controlled, cross-over study was conducted in which magnesium sulphate was administered as an i.v. infusion. Spontaneous pain was recorded and qualitative sensory testing with cotton wool was performed in seven patients with postherpetic neuralgia before and after the i.v. administration of either magnesium sulphate 30 mg kg^{-1} or saline.

Results. During the administration, pain scores were significantly lower for magnesium compared with placebo at 20 and 30 min (P=0.016) but not at 10 min. I.V. magnesium sulphate was safe, well-tolerated and effective in patients with postherpetic neuralgia.

Conclusion. The present study supports the concept that the *N*-methyl-D-aspartate receptor is involved in the control of postherpetic neuralgia.

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Postherpetic neuralgia (PHN) is characterized by pain that persists for more than a month after the healing of acute herpes zoster (HZ) lesions.[1] It represents an increasing clinical problem in the elderly population, with a prevalence reaching 75% in patients over 70 yr who have previously had HZ infection.[2]

The typical features of PHN are burning, aching or itching and continuous pain, with additional sharp and shooting components, often associated with hyperalgesia and allodynia. PHN is the consequence of the extensive peripheral and spinal damage caused by the reactivation of the dormant virus.[3] Continuous activation of C-nociceptor fibres causes the release of glutamate from central terminals acting on the amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and the *N*-methyl-D-aspartate (NMDA) receptor.[4]

The NMDA receptor plays an important role in the mechanisms underlying central sensitization (wind-up) in the spinal cord and is critically important for the establishment of several chronic neuropathic pain states.[5] In its inactive state, it is blocked by the presence of a centrally positioned magnesium ion.[6] Afferent activity in nociceptor fibres dislodges the central magnesium ion from the NMDA receptor, thus allowing calcium influx into the cell.

The NMDA receptor antagonist ketamine reduces neuropathic pain and allodynia in patients with chronic PHN.[7] However, the psychomimetic side-effects limit its use in clinical practice.[8]

Magnesium has been shown to exert a physiological block of the ion channel on the NMDA receptor, preventing extracellular calcium ions from entering the cell and contributing to secondary neuronal changes.[9] This double-blind, placebo-controlled, cross-over study evaluated the analgesic properties of magnesium sulphate in patients with PHN.

Methods

Seven patients with PHN, who had not previously responded to conventional treatment with anticonvulsants

Table 1 Individual patient characteristics. P=placebo; M=magnesium sulphate

Age (yr)	Gender	Group	Ethnicity	HZ (yr)	PHN	Pain	Dynamic allodynia
76	F	P/M	Caucasian	3	Lumbar	+	–
53	F	P/M	Caucasian	4	Thoracic	+	+
76	M	P/M	Caucasian	1.5	Trigeminal	+	–
69	M	M/P	Black	3	Thoracic	+	+
81	F	P/M	Caucasian	0.9	Thoracic	+	+
76	F	M/P	Caucasian	0.8	Cervical	+	+
61	F	P/M	Caucasian	0.9	Thoracic	+	+

Table 2 Pain scores for the difference between magnesium and placebo within individuals at baseline and 10, 20 and 30 min for the seven patients. The 95% confidence interval is that for the median difference between placebo and magnesium within individuals

	Baseline	10 min	20 min	30 min
Mean	0.0	1.9	2.4	3.1
Standard deviation	1.00	1.95	1.81	2.48
Median	0	1	2	2
Minimum	–2	0	1	1
Maximum	1	5	5	7
95% confidence interval		0–5	1–5	1–7
P value		0.063	0.017	0.017

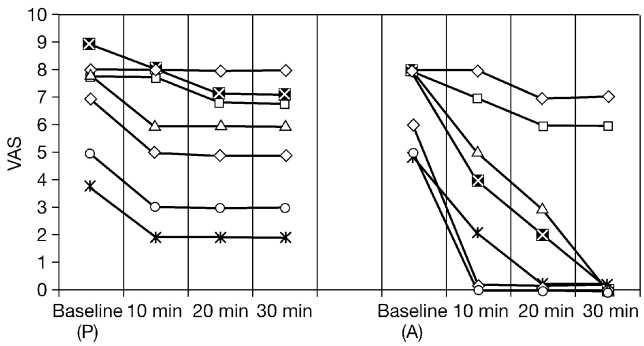

Fig 1 Individual pain scores for the seven patients during the 30 min infusion of placebo (P) and magnesium (A).

and tricyclic antidepressants, were assigned randomly to receive magnesium sulphate first and placebo second or vice versa with a wash-out period of 1 week in between. Randomization was achieved with random number tables. Saline and magnesium solutions were similar in appearance and volume. Both the patient and the assessor were blinded to treatment. The study protocol was approved by the Hospital Ethical Committee and by the Medicines Control Agency of the UK, and informed patient consent was obtained.

Patients with cardiac failure (New York Heart Association grade III or IV), atrioventricular conduction block (grade II or III), serum creatinine in excess of 110 mol litre^{-1} and severe liver disease were excluded from the study. Subjects above 18 yr of age with PHN for more than 3 months after healing of the HZ rash and showing a pain score of $\geqslant$4 on a numerical visual analogue scale (VAS) (0=no pain, 10=worst possible pain) were assigned randomly to receive either an i.v. infusion of 0.9% saline 100 ml or magnesium sulphate 30 mg kg^{-1} (magnesium 0.06 mmol kg^{-1}) over 30 min (the required amount was added as a 50% magnesium sulphate solution to 100 ml of saline). One week later, the other solution was infused. The magnesium concentration used in the study was well below what is widely administered in suspected myocardial infarction, for the emergency treatment of serious arrhythmias and to prevent recurrent seizures in eclampsia.

The severity of pain was recorded using a numeric VAS at baseline and at 10, 20 and 30 min during the infusion. The patients were also asked about the degree of pain relief at the time of discharge, 1 h later and the following morning. Mechanical stimulation with cotton wool to test for mechanical dynamic allodynia was performed before and immediately after the infusions. Serum magnesium concentrations were measured before the start of the study and found to be within normal limits in all patients.

The Wilcoxon signed rank test was used to ascertain if pain scores were the same between magnesium and placebo within individuals, sequentially in time, at 10, 20 and 30 min during the infusion. As three sequential statistical tests were performed, Bonferroni's correction factor was applied to adjust for multiple testing. The critical significance level was adjusted from 0.05 to 0.017 accordingly. All reported *P*-values are two-tailed.

Results

Patient characteristics are shown in Table 1. The minimum duration of PHN in our sample was 8 months.

The mean (SD) pain score during the magnesium infusion fell from 6.7 (1.7) at baseline to 1.9 (3.2) at 30 min. The difference in pain score between placebo and magnesium within individuals was not significant at 10 min (P=0.063) but was significant at 20 (P=0.016) and 30 min (P=0.016) (Table 2). Five out of seven patients reported complete pain relief after the magnesium infusion and none after the saline infusion (Fig. 1), which lasted until hospital discharge 1 h later. The patients were contacted by telephone the following day. All of them reported that the pain had come back during the previous evening. The same five patients who

achieved pain relief had dynamic allodynia, which was unchanged after either infusion.

No adverse events were reported during the magnesium sulphate infusion, apart from a mild feeling of warmth at the site of the injection. Throughout the magnesium infusion, heart rate and arterial blood pressure did not change by more than 15% of baseline values for all patients. Arterial oxygen saturation was stable and did not fall below 97%.

Discussion

Postherpetic neuralgia is a condition that is not always responsive to established treatments, such as antidepressants, antiepileptics and opioids. Furthermore, fewer than 50% of patients with PHN experience pain relief in the absence of unacceptable adverse effects.[10] The pathophysiology of PHN includes both peripheral and central mechanisms. Three subtypes of PHN have been proposed recently: (i) deafferented allodynic; (ii) deafferented non-allodynic; and (iii) irritable nociceptor.[11] Additionally, patients may also present static (pressure-evoked) and/or dynamic (brush-evoked) allodynia. Our patient population was small and not a representative sample of the three subgroups. Therefore, it was not possible to look for selective effectiveness of magnesium between the above subtypes.

Magnesium could be expected to modulate neuropathic pain by blocking the NMDA receptor calcium ionophore. This mechanism may prevent nociceptive-associated central sensitization[5] and lessen the increased activity of wide-dynamic range neurones in the dorsal horn after prolonged activation. Assuming extracellular distribution of magnesium, plasma concentrations in our patients would have risen by approximately a third during the infusion, causing a block of the NMDA receptor with subsequent pain relief.

Magnesium therapy has been shown to be potentially beneficial in eclampsia[12] and, more recently, in headache[13 14] and acute migraine attacks.[15] The systemic and intrathecal injection of magnesium suppresses neuropathic pain responses in different rat models.[15–21] In man, an i.v. infusion of magnesium sulphate caused a reduction of postoperative analgesic requirement[22–24] and an oral daily dose of magnesium sulphate was shown to be effective in neuropathic pain.[25]

In our study, magnesium clearly reduced PHN pain in comparison with placebo. This effect was initially observed 10 min after the start of the infusion, reaching statistical significance after 20 min. The majority of subjects achieved substantial pain relief during the magnesium infusion, whereas none of them had any relief during the placebo infusion. Although the study had a small sample size, its cross-over design increased its statistical power.

We did not observe an inhibitory effect on allodynia, as would have been predicted from postsynaptic action of magnesium. However, dynamic allodynia does not rely on the wind-up effect, which is mediated through the NMDA receptor. It is therefore not surprising that there was a different response to i.v. magnesium between ongoing pain and pain caused by brief mechanical stimulation.

Our results show that the physiological action of magnesium on NMDA receptors can be translated into a viable concept for pain control in some patients with PHN.

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