Intravenous Magnesium Sulfate Relieves Cluster Headaches in Patients With Low Serum Ionized Magnesium Levels

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Accepted for publication June 25, 1995.

Patients with cluster headaches have been reported to have low serum ionized magnesium levels. We examined the possibility that patients with cluster headaches and low ionized magnesium levels may respond to an intravenous infusion of magnesium sulfate. Thirty-eight infusions of magnesium sulfate were given to 22 patients with cluster headaches. The mean ionized magnesium level prior to 23 infusions which provided relief for at least 2 days and enabled the patient to skip two or more attacks, was 0.521 ± 0.016 mmol/L; this value was 0.561 ± 0.016 prior to 15 infusions which were ineffective. These latter 15 infusions were preceded by higher total magnesium levels. The ionized magnesium level prior to the 23 effective infusions was below 0.54 mmol/L in 19 patients. Five of the 15 ineffective infusions were accompanied by basal ionized magnesium levels below 0.54 mmol/L. In 76% of the infusions, there was a correlation between a response and an ionized magnesium level below 0.54 mmol/L. Nine patients (41%) obtained clinically meaningful improvement. Spontaneous remissions and a placebo effect might have accounted for some of the improvement. However, this should have applied equally to all patients, regardless of the ionized magnesium level. Measurements of ionized magnesium may prove useful in elucidating the pathogenesis of cluster headache and in identifying patients who may benefit from treatment with magnesium.

Key words: cluster headache, treatment, serum ionized magnesium, magnesium sulfate infusion

Abbreviations: TMg total magnesium, IMg^{2+} ionized magnesium, Mg magnesium, CH cluster headache, $MgSO_4$ magnesium sulfate

(*Headache* 1995;35:597-600)

Low total magnesium (TMg) levels have been found, albeit inconsistently, in the serum and various cells of headache patients.[1-4] In vivo ^{31}P nuclear magnetic resonance spectroscopy, during and between migraine attacks, revealed decreased whole brain magnesium (Mg) content.[5] Inconsistency between reports on the serum and intracellular magnesium levels in headache patients may be attributable to the fact that TMg, rather than the biologically active ionized magnesium (IMg^{2+}), levels were being measured.[6] Recently, it has become possible to measure the serum IMg^{2+} levels.[7-9]

We have reported that 12 of our patients with episodic cluster headache (CH) had a mean IMg^{2+} level significantly lower than both controls and 4 patients with chronic CH.[10] Total magnesium levels in these patients were not different from those found in controls.

In a study of 40 patients with an acute migraine attack, we found that of 21 patients with IMg^{2+} levels less than 0.54 mmol/L, 18 responded (no recurrence in 24 hours) to an intravenous infusion of 1 g of magnesium sulfate ($MgSO_4$).[11] Of the 19 patients with IMg^{2+} levels above 0.53 mmol/L, only 3 responded. Mean IMg^{2+} levels of responders and non-responders were significantly different, while the TMg levels were not.

In this study, we examined the possibility that patients with CH and low IMg^{2+} may also respond to an intravenous infusion of $MgSO_4$.

METHODS

All patients with CH seen at the New York Headache Center during their cluster were asked to consent to participate in this study. The diagnosis of CH was established using the IHS classification.[12]

An intravenous infusion of 1 g $MgSO_4$ was given in a 10% solution over a period of 5 minutes with patients in a recumbent position. If a patient had relief for at least 2 days and skipped two or more expected attacks, repeated infusions of 1 to 2 g $MgSO_4$ were given. Patient 16 had two infusions on the same day because the first infusion produced dramatic relief of an acute headache, but hours later he developed another headache for which a second infusion was given.

Immediately prior to each infusion, and in some patients at other times, 5 mL of blood was drawn anaerobically to maintain a normal pH. An ion-selective electrode for Mg^{2+} was used to measure serum IMg^{2+} levels.[7-9] Total magnesium in the serum was determined with Kodak DT-60 Ektachem Analyzer.[7-9] Mean values ± SEM were calculated and compared for statistical significance by a nonpaired Student's *t*-test, ANOVA, and Scheffe's contrast test, where appropriate. A *P* value of less than 0.05 was considered significant.

This was not a double-blind study, but the laboratory per-

Table 1.—Clinical and Laboratory Data on 22 Patients With Cluster Headache Who Received Magnesium Infusions

Patient	Sex	Age, y	Date	Magnesium Sulfate, g	Correlation*	Ionized Magnesium, mmol/L	Total Magnesium, mmol/L	Relief, days	Duration of Current Cluster, weeks	Average Duration of Prior Attacks, weeks
1	M	40	5/2	1	---	N/A	N/A	2	55	---
			5/16	1.5	Y	0.44	0.82	2		
			5/26	2	Y	0.48	0.90	2		
			6/20	2	Y	0.47	0.90	2		
			7/11	2	Y	0.52	0.90	2		
			7/25	2	Y	0.54	0.99	0		
			8/13	2	N	0.53	0.90	0		
			10/18	0	N	0.52	0.78	---		
2	F	32	6/20	1	Y	0.45	0.86	120+	5	6-12
			7/19	0	---	0.45	0.78	---		
			8/16	0	---	0.47	0.78	---		
			10/18	0	---	0.48	0.74	---		
3	M	35	4/29	1	Y	0.52	0.82	180+	4	12-16
			5/29	0	---	0.54	0.95	---		
4	M	46	7/12	1	Y	0.49	0.82	3	0.5	4-8
			7/19	2	Y	0.50	0.86	20		
			8/15	2	Y	0.52	0.86	5		
			8/22	2	Y	0.51	0.90	5		
			8/29	2	Y	0.53	0.82	120+		
5	M	39	7/14	1	N	0.54	0.86	2	1	8-12
			7/16	1	Y	0.55	0.82	0		
6	F	47	7/16	1	N	0.50	0.95	2	1	16
			7/19	2	N	0.53	0.82	0		
7	M	29	7/20	1	N	0.53	0.82	1	6	2-3
			7/22	1	N	0.50	0.74	0		
8	M	40	7/27	1	Y	0.55	0.86	0	4	8
9	M	37	8/18	1	N	0.51	0.86	1	2	4
10	F	34	9/1	1	Y	0.54	0.86	1	75	---
11	M	40	8/4	1	Y	0.52	0.82	6	1	6-8
			8/10	1	Y	0.47	0.74	7		
			8/24	1	Y	0.49	0.78	7		
12	M	40	8/4	1	Y	0.54	0.82	0	4	2-8
13	F	34	8/24	1	Y	0.52	0.82	7+	4	2-8
14	F	25	8/31	1	N	0.55	0.78	2	2	3
15	F	50	9/26	1	Y	0.53	0.86	30+	4	1st**
			10/25	0	---	0.56	0.99	—		
16	M	22	10/13	1	Y	0.58	0.86	0	1	1st**
			10/13	1	Y	0.76	1.19	0		
17	M	25	10/13	1	Y	0.53	0.82	90+	2	3
			10/21	5	---	0.47	0.74	---		
18	M	29	10/20	1	Y	0.49	0.78	90+	3	1st**
19	M	43	11/2	1	Y	0.55	0.82	0	16	2
20	M	36	11/15	1	Y	0.59	0.99	0	2	2-3
			11/17	1	Y	0.61	0.99	0		
21	F	32	1/6	1	Y	0.46	0.74	21+	25	8-12
22	M	37	1/11	1	N	0.56	0.90	2	4	4-6

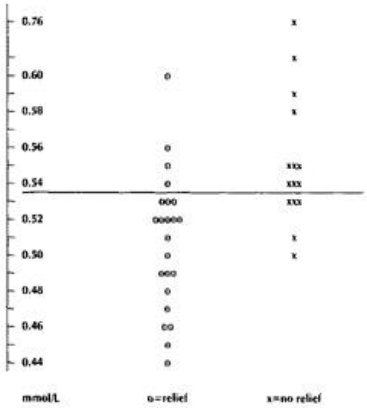
*Y indicates correlation present or N correlation absent between ionized magnesium levels below 0.54 mmol/L and relief.
**First cluster.

sonnel were blinded in that no clinical information or patient identification accompanied the serum samples. The clinician administering the infusions (AM) did not receive any laboratory results for 1 to 2 weeks. In patients 1, 4, and 11 the third and subsequent infusions were given with the knowledge of the previous serum IMg^{2+} levels.

RESULTS

Seven women and 15 men were enrolled. Their ages ranged between 22 and 50 years (mean age 36). Two patients had chronic cluster headache and 20 had episodic CH. A total of 39 infusions were given. The serum from the first infusion in patient 1 was not tested, and this infusion was not included in any of the calculations. Patient 11 left the country and was unable to return for another infusion; his headaches resolved spontaneously after a week of headaches, following 7 days of relief after the third infusion. Twenty-three infusions in 14 patients resulted in improvement lasting at least 2 days with skipping of at least two expected attacks (Table 1). In nine patients, the infusions produced either a sustained complete remission (patients 2, 3, 13, 15, 17, 18, and 21) or provided days to weeks of relief until complete remission occurred (patients 4 and 11). Overall satisfaction with the treatment was very high in those nine patients.

The mean IMg^{2+} level prior to infusions that resulted in improvement was 0.521 ± 0.016 mmol/L (P<0.001), compared to controls, while the mean IMg^{2+} level prior to infusions that did not result in improvement was 0.561 ± 0.016 mmol/L (P>0.05) (Figure, Table 2). Corresponding TMg levels were 0.840 ± 0.011 and 0.889 ± 0.029 mmol/L, respectively.



Serum ionized magnesium levels in patients with cluster headache prior to magnesium sulfate infusions.

Table 2.-Laboratory Data Obtained Prior to Infusions of Magnesium Sulfate for the Treatment of Cluster Headache

	No. of Patients	Ionized Magnesium, mmol/L	Total Magnesium, mmol/L
Controls	66	0.60 ± 0.008	0.82 ± 0.009
Relief	23	0.521 ± 0.016*	0.840 ± 0.011
No relief	15	0.561 ± 0.016	0.889 ± 0.029**

Values are mean ± SEM.
*P<0.001 compared to controls.
**P<0.05 compared to controls.

The nonresponding group had basal serum TMg levels significantly greater than controls (P<0.05). Ionized magnesium levels below 0.54 mmol/L preceded 19 of the 23 infusions that resulted in relief and 5 of 15 infusions that were found to be ineffective. Thus, there was a high correlation between IMg^{2+} levels below 0.54 mmol/L and clinical response in 76% of infusions (P<0.01). The only side effect observed was that of a flushed feeling during all infusions.

COMMENTS

Cluster headaches in the past have been grouped together with migraines under the rubric of vascular headaches, in part because of many similar features. However, many aspects of the disease of cluster headache are clearly different from migraine headache. Strict periodicity, daily nocturnal occurrence, extreme intensity, and responsiveness to oxygen, corticosteroids, and lithium are some such distinguishing features.

The mechanism by which magnesium deficiency may be involved in the pathogenesis of migraines has been proposed.[13] It was suggested that propensity to cerebral vasoconstriction in conditions of Mg deficiency[14,15] may be an important factor in the development of migraines. The precise effect of Mg deficiency on migraine headaches remains obscure; even less data exists about cluster headaches. Possible areas of Mg influence related to headaches include its known effects on serotonin receptors,[16-18] nitric oxide production,[19] NMDA receptors,[20-22] catecholamine production and activity,[23] and a large number of enzymatic processes.[24]

The serotoninergic drug, sumatriptan, is effective for both migraine and cluster headaches, which suggests serotonin receptors as the likely site of action of magnesium in these headache types.

Neurogenic inflammation is a popular theory of migraine pathogenesis where the effect of substance P plays a prominent role.[25] Substance P has been shown to be generated and released in experimentally-induced Mg deficiency.[26]

Clinically significant relief occurred in 9 of our 22 patients (41%). However, the actual proportion of patients that may benefit from treatment with magnesium could be lower because of two factors. A placebo effect is one such factor. However, in cluster headaches it is probably much less pronounced than in any other headache type because of its strict nocturnal periodicity and because of the extreme intensity of pain. The second factor is the fact that some of our patients who responded to magnesium sulfate infusions might have gone into spontaneous remissions. In patients 4 and 11, this is clearly the case. They both had the usual duration of their cluster, nevertheless, $MgSO_4$ infusion seemed to have been of significant benefit in both as it provided days to weeks of relief. Finally, spontaneous remissions might have been expected to occur regardless of IMg^{2+} levels.

Persistence of depressed serum IMg^{2+} levels during remission in patients 2 and 17 suggests that Mg deficiency may be only one of the predisposing factors leading to the development of CH. However, in patients 3 and 15, IMg^{2+} levels remained elevated during remission.

Our findings suggest that measurements of serum IMg^{2+} may prove useful in elucidating the pathogenesis of CH and in identifying patients who may benefit from treatment with magnesium.

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