MAGNESIUM

Magnesium and Headaches

Magnesium administered orally or by slow infusion in the office is a safe and effective treatment for migraine headache. It helps to prevent migraine in the magnesium-deficient person, and is particularly useful for patients who experience menstrual headaches. Magnesium infusion administered in our office can also be used to abort a severe migraine in progress. (Infusion is covered by some insurers.)

(Review article for physicians and patients seeking further information.)

Magnesium is the second most abundant intracellular cation. It is the fourth most plentiful metal in the body. One to five percent of magnesium is in the extracellular fluid, 34 to 45 percent are intracellular and over 50 percent is contained in the mineral phase of the skeleton. About 75 percent of the serum magnesium is ionized, while the rest is protein-bound. Magnesium is an essential intracellular element and is involved in a large number of cell functions. Despite the recognition of its essential functions in the body, cardiovascular effects of magnesium deficiency, magnesium's role in the development of fetal brain, and its relaxing effect on smooth muscle in patients with asthma have been only recently widely acknowledged.

Many studies of the role of magnesium in the pathogenesis of migraines looked at the intracellular magnesium content and they have produced conflicting results. This may be because intracellular magnesium content seems to be stable despite wide fluctuations in serum magnesium. Other studies examined the total serum levels of magnesium while it is the ionized portion that exerts al the physiological effects. The development of a specific ion-selective electrode for magnesium has made it possible to accurately and rapidly measure serum ionized magnesium levels in patients with various headache types (1,2). We have found that of 500 patients with various headache syndromes, 29% had levels of ionized magnesium below 0.54 mmol/L (normal adult lMg2+ ranges from 0.54 to 0.65 mmol/L, 95% CI). During an acute migraine attack, 50% of the patients have this abnormality (3).

Recent discoveries of the role of magnesium in the development of headaches are finally beginning to lead to large clinical trials. For many years, magnesium deficiency has been suspected to play a role in the pathogenesis of migraine. A prospect for simple, safe and cheap therapy has been alluring, but has produced much skepticism.

A theoretical basis for the role of magnesium deficiency in headaches was first proposed in 1985 (4). Over the past decade a great deal has been learned regarding the effects of magnesium on a variety of brain neurotransmitters,

enzymes and metabolism. These effects fit well into the several hypotheses of pathogenesis of migraines that have been proposed over the years.

One of the leading theories of migraine proposed by Jes Olesen considers nitric oxide to be the earliest neurotransmitter activated in the cascade of events leading to a migraine attack (5). This theory has considerable experimental support and drugs are being developed that can block nitric oxide synthase, which in turn might abort migraine attacks. It has been clearly established that nitric oxide production can be modulated by changes in magnesium concentration (6).

Another popular theory of migraine that so far has only experimental support (animal studies) is that of neurogenic inflammation (7). This theory suggests that inflammation of cranial blood vessels, mediated by the trigeminal nerve system, is responsible for the phenomenon of migraine. Substance P plays an important role in this theory and its release has been shown to be regulated by magnesium concentration as well (8).

Serotonin is known to be released from platelets during a migraine attack, to be a potent cerebral vasoconstrictor and to promote nausea and vomiting. A lowering of serum IMg2+ and an elevation of the serum ICa2+/IMg2+ ratio may increase affinity for serotonin cerebral vascular muscle receptor sites, potentiate cerebral vasoconstriction induced by serotonin (9) and facilitate 5-HT release from neuronal storage sites (10).

Activation of a 5HT1B/1D serotonin receptor subtype by sumatriptan, and other drugs, effectively aborts migraine attacks in the majority, but not all migraine sufferers. Although serotonin receptors may not be involved at the earliest stage of a migraine attack, this clinical effect of sumatriptan confirms the crucial role of serotonin receptors in migraines.

Platelet aggregation with subsequent serotonin release has been shown to be present during migraine attacks (11). Magnesium has been shown to cause a dose-dependent inhibition of platelet aggregation (12).

Magnesium has a strong vascular dilating effect (13), lending support to the vascular theory of migraine. IMg2+ levels are known to affect entry of Ca2+, and intracellular ICa2+ from sarcoplasmic and endoplasmic reticulum, in vascular smooth muscle and vascular endothelial cells and to control vascular tone and reactivity to endogenous hormones and neurotransmitters (13,14). Cerebral blood vessel muscle cells are particularly sensitive to IMg2+; Mg deficiency results in contraction and potentiation of vasoconstrictors and excess IMg2+ results in vasodilatation and inhibition of vasoconstrictors (15).

Magnesium is intimately involved in the control of N-methyl-D-aspartate (NMDA) glutamate receptors which play an important role in pain transmission in the

nervous system (16) and regulation of cerebral blood flow (17). Magnesium ion plugs the NMDA receptor and prevents calcium ions from entering the cell. Lowering Mg2+ concentration facilitates activation of the NMDA receptor, which allows calcium to enter the cell and exert its effects both on neurons and cerebral vascular muscle. Thus magnesium can be considered an NMDA receptor antagonist at several important sites.

A strong family history is present in up to 80% of patients with migraines (18). This fact along with the identification of a gene for familial hemiplegic migraine (19) suggests that genetic factors are present in a majority of migraine patients. Cellular magnesium content and magnesium metabolism are also under genetic control (20). It is possible that there is an overlap between these two genetic mechanisms.

Magnesium deficiency appears to be a common denominator in all leading theories of migraine pathogenesis. However, the wide range of effects makes it difficult to pinpoint where magnesium's influence is most crucial in the development of migraine headaches. It is likely that many, if not all of these effects are important. Magnesium deficiency is clearly not the cause of all migraines since we found that only 50% of patients with an acute migraine attack have low serum ionized magnesium levels and respond to magnesium therapy. It is likely that it is a strong predisposing (genetic?) factor for half of the patients. However, it appears that no other current theory can completely explain the pathogenesis of migraines. Even sumatriptan which provided the strongest clinical support for the serotonin theory has an efficacy rate of about 70%. Non-serotonin mechanisms could be operational in the other 30% of patients. Migraine appears to be a heterogeneous disorder that possibly has several different mechanisms leading to a similar clinical expression.

Clinical Studies

Several studies have shown lowered red blood cell total magnesium content in patients with migraines, although one study did not confirm this finding. In two reports total serum Mg levels were found to be decreased in migraine patients (21,22). Two other studies showed normal serum levels of total Mg between attacks of migraine (23,24). One of these studies demonstrated decreased total Mg concentration in leukocytes (24), while the other one found decreased Mg concentration in lymphocytes and polymorphonuclear cells, but not erythrocytes (23). Investigation using in vivo 31P nuclear magnetic resonance spectroscopy showed low brain Mg during and between migraine attacks in a few subjects (25).

Two double-blind, placebo controlled trials showed therapeutic efficacy of Mg supplementation in headache patients. The first one was a double-blind placebo-controlled study of oral magnesium supplementation in 24 women with menstrual migraine yielding positive results (23). The supplement

consisted of 360 mg of magnesium pyrrolidone carboxylic acid taken in 3 divided doses. In addition to a significant reduction of the number of days with headache, patients receiving active treatment also showed improvement of the Menstrual Distress Questionnaire score. Four patients dropped out of the study, but only one due to side effects (magnesium-induced diarrhea).

A larger double-blind, placebo-controlled, randomized study involving 81 patients with migraine headaches also showed significant improvement in patients on active therapy (26). Attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group. The active treatment group received 600 mg of trimagnesium dicitrate in a water soluble granular powder taken every morning. Diarrhea was present in 18.6% and gastric irritation in 4.7% of patients in the active group; three patients dropped out of the study.

We have conducted a 40-patient trial of intravenous magnesium sulfate for the treatment of acute migraine attacks (3). At the time of infusion a blood sample was obtained for serum IMg2+ levels. All patients received active treatment, but both the clinician and the patients were blinded to the serum IMg2+ levels since the clinical evaluation was completed long before the laboratory measurements were done. An 85% correlation between the clinical response and the serum IMg2+ levels was found ($p<0.01$). Of the 21 patients who had serum IMg2+ levels below 0.54 mmol/L 18 (86%) had a sustained (over 24 hours) relief of their pain and associated symptoms. Among 19 patients with levels above 0.54 mmol/L only 3 (16%) had such relief.

Although the study was not double-blind placebo controlled, neither the clinician nor the patients knew IMg2+ levels until long after the clinical assessment. The placebo effect should have affected both groups equally.

We also looked at the effect of intravenous magnesium on patients with cluster headaches. Double blind-studies of cluster headaches are difficult to conduct because of the self-limiting nature of this condition and a relative infrequency of this condition. In an open-label study we administered 1 gram of magnesium sulfate to 22 patients with cluster headaches. Forty percent of patients obtained meaningful relief, that lasted for more than 2 days. In some patients a single infusion aborted a cluster before the expected spontaneous remission (based on previous attacks). A correlation was found between serum IMg2+ and clinical response (27).

In most cases it is impractical to treat migraine attacks with an intravenous infusion of magnesium sulfate. However, oral prophylactic magnesium supplementation may be beneficial for a significant proportion of patients with frequent migraine headaches. Wider availability of serum IMg2+ measurements will allow for selection of patients who are most likely to respond to this treatment. Studies comparing absorption of various

magnesium salts and preparations are needed because many available magnesium preparations are poorly absorbed. We suspect that amino acid chelated magnesium and slow release forms of magnesium tend to be better absorbed and we recommend those to our patients. However, we have seen both poor absorption and laxative effect from these preparations as well. Our current recommendation is for patients to try oral magnesium supplementation with 400 mg of chelated or slow release preparation, along with our other standard abortive therapy, used as needed.

In women with menstrual migraines who do not respond to oral supplementation, we recommend giving an infusion of 1 gram of magnesium sulfate in a 10% solution of normal saline within a week of their menstruation. If this infusion prevents their menstrual migraine, a higher dose and possibly a different salt of magnesium is given orally on a daily basis. We have encountered a few women who do not obtain any benefit from a large dose (up to 800mg) of oral magnesium and prefer to receive monthly infusions of magnesium sulfate. Patients with non-menstrual migraines can be also given an infusion of magnesium sulfate on as needed basis, if they do not improve with oral magnesium or develop gastrointestinal side effects (most commonly diarrhea or stomach pains). In our patients, the interval between infusions ranges from once a month to once every 3 months. The majority of patients can be supplemented orally and do not require infusion. Having access to an ion-selective electrode allows us to pursue magnesium therapy very selectively, only in patients with documented deficiency.

Patients must be cautioned about excessive intake of magnesium. Diarrhea usually prevents absorption of magnesium to toxic levels, but such a possibility clearly exists, especially in patients with impaired renal function. Magnesium intoxication can lead to loss of deep tendon reflexes, followed by muscle weakness and with increasing levels can lead to cardiac muscle weakness and respiratory paralysis, which may lead to death. Anecdotal reports of safe and effective daily intake of up to 2 grams of magnesium salts should not make anyone assume that this is a safe dose. In some patients, who have only partial absorption this may be a safe and effective dose, while in others it may lead to toxicity. In patients taking large amounts of oral magnesium, total magnesium level measurements are useful in monitoring for potentially toxic levels.

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