Magnesium for Migraine
Rationale for Use and Therapeutic Potential

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Summary

Magnesium deficiency can be assessed using serum ionised magnesium level, which appears to be a much more sensitive indicator of magnesium status than total serum or intracellular levels of this ion. In vitro and in vivo studies indicate that magnesium deficiency could play a contributing role in the pathogenesis of migraine in up to 50% of patients. In support of these findings, results from a single study indicate that intravenous infusion of magnesium sulfate can produce prompt and sustained relief of a migraine attack in half of patients. In this study, 85% of responders had low serum ionised magnesium levels, while 85% of non-responders had normal levels. Prophylactic oral magnesium supplementation has been shown to be effective in 2 double-blind trials, but ineffective in another. A possible reason for the lack of response reported in the latter study could be poor absorption of magnesium from the preparation used. Chelated magnesium diglycinate appears to be one of the better absorbed preparations.

Despite the absence of definitive large scale studies, we recommend magnesium supplementation (chelated magnesium diglycinate 600 mg/day) in patients who experience migraine. This recommendation is based on the excellent safety profile and low cost of the supplementation, and the large amount of experimental and clinical data that support the use of this therapy.

Magnesium is an essential intracellular element that is involved in a large number of cell functions. However, despite the vital importance of this element, relatively little research has been done on its role in various diseases. The cardiovascular effects of magnesium deficiency, the role of magnesium in the development of the fetal brain, and the relaxing effect of the ion on smooth muscle in patients with asthma have only recently been widely acknowledged. [1-3]

The role that magnesium plays in the development of headaches has also been recently defined, and this has begun to lead to large clinical trials of magnesium as a therapy for headache.

For many years, magnesium deficiency has been suspected as playing a role in the pathogenesis of migraine. As a simple, well tolerated and inexpensive therapy for migraine, magnesium is an alluring choice, but there has been much scepticism about its use. One of the impediments to progress in this area has been the lack of a reliable and simple measure of magnesium content in soft tissues. Many researchers have measured total magnesium levels in various tissues, but the published results have been inconsistent (see section 2.1).

We believe that the reason for this inconsistency has been the fact that total magnesium levels have been measured, but it is the ionised form of magnesium (IMg++) that actually exerts the physiolog-
ical effects. The development of a specific ion-selective electrode for magnesium has made it possible to accurately and rapidly measure serum IMg++ levels in patients with various headache types.\[4,5\] We have found that of 500 patients with various headache syndromes, 29% had levels of IMg++ below 0.54 mmol/L\[6\] (normal adult IMg++ ranges from 0.54 to 0.65 mmol/L, 95% confidence interval).\[4,5\] In our study of 40 patients with an acute migraine attack, 50% of the patients had this abnormality.\[7\] Based on the measurements of serum IMg++ levels we have suggested that the disputed entity of chronic daily headaches can be subdivided into chronic migraine and chronic tension-type headaches. Patients with chronic migraine headaches have a much higher incidence of low serum IMg++ level than patients with chronic tension-type headaches.\[8\]

1. Potential Role of Magnesium in the Current Theories of Migraine Pathogenesis

A theoretical basis for the role of magnesium deficiency in the pathogenesis of headaches was first proposed in 1985.\[9\] Over the past decade, a great deal has been learned regarding the effects of magnesium on a variety of brain neurotransmitters and enzymes and on brain 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, as proposed by Olesen and colleagues,\[10\] considers nitric oxide (NO) to be the vasoactive substance and neurotransmitter that is activated early in the cascade of events leading to a migraine attack. This theory has considerable experimental support\[11\] and drugs are being developed that can block NO synthesis (NO synthase inhibitors),\[11\] which in turn might abort migraine attacks. It has been clearly established that NO production can be modulated by changes in magnesium level, i.e. low magnesium would be expected to inhibit production of NO.\[12\]

Another popular theory of the pathogenesis of migraine, that so far has only experimental support (i.e. animal studies), is that of neurogenic inflammation.\[13\] 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.\[14\] Low levels of magnesium would be expected to increase the release of substance P and hence potentiate constriction of cerebral vessels.

Serotonin (5-hydroxytryptamine; 5-HT) is known to: (i) be released from platelets during a migraine attack; (ii) be a potent cerebral vasoconstrictor; and (iii) promote nausea and vomiting. A lowering of serum IMg++ level and an elevation of the serum ratio of ionised calcium (ICa++*) to IMg++ may increase the affinity for cerebral vascular muscle serotonin receptor sites, potentiate cerebral vasoconstriction induced by serotonin\[15\] and facilitate serotonin release from neuronal storage sites.\[16\] The serotonin 5-HT1B/1D receptor agonist sumatriptan, and other drugs with a similar mechanism of action, effectively abort migraine attacks in the majority of, but not all, migraineurs. 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 migraine.

Platelet aggregation, with subsequent serotonin release, has been shown to occur during migraine attacks.\[17\] Magnesium has been shown to cause a dose-dependent inhibition of platelet aggregation.\[18\]

In an in vitro study, magnesium was shown to have a strong vascular dilating effect\[19\] lending support to the vascular theory of migraine. IMg++ levels are known to affect the entry and release of calcium and intracellular ICa++* into the sarcoplasmic and endoplasmic reticulum, in vascular smooth muscle and vascular endothelial cells, and to control vascular tone and reactivity to endogenous hormones and neurotransmitters.\[19,20\] Cerebral blood vessel muscle cells are particularly sensitive to IMg++ level; magnesium deficiency results in vasoconstriction and potentiation of the effects of...