Magnesium as an Effective Adjunct Therapy for Drug Resistant Seizures

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ABSTRACT: Objective: To explore the use of magnesium (Mg), an endogenous ion and enzymatic co-factor used in a variety of medical applications, for the treatment of epileptic seizures resistant to traditional medical therapy. Background: For almost a century, Mg has been used as prophylaxis and treatment of seizures associated with eclampsia. Mg is a CNS depressant, with numerous functions intracellularly and extracellularly. However, because of the availability of well studied anticonvulsant drugs, Mg has not been tested widely in the treatment of epileptic seizures. Methods: A retrospective chart review of 22 cases of drug resistant epilepsy, where a trial of empiric oral Mg supplementation (mainly in the form of Mg-oxide) was conducted. Results: Oral Mg supplementation was associated with a significant decrease in the number of seizure days per month, from 15.3 ± 13.2 (mean ± SD) to 10.2 ± 12.6 at first follow up (3-6 months, p=0.021), and to 7.8 ± 10.0 seizure days/month at second follow up (6-12 months, p=0.004). Thirty-six percent had a response rate of 75% or greater at second follow-up. Two patients reported seizure freedom. Most patients were well maintained on MgO 420mg twice a day, or in 2 cases, Mg Lactate, without significant adverse effects, the most frequent being diarrhea (4/22). Discussion: These results suggest that oral Mg supplementation may prove to be a worthwhile adjunctive medication in treating drug intractable epilepsy. Conclusions: A prospective, double-blinded, placebo controlled study is warranted to evaluate the potential of Mg for the treatment of drug-resistant seizures.

RÉSUMÉ: Le magnésium comme traitement d’appoint efficace dans les crises convulsives résistantes au traitement. Objectif : Le but de l’étude était d’explorer l’utilisation du magnésium (Mg), un ion endogène et un cofacteur enzymatique ayant différentes applications en médecine, dans le traitement des crises épileptiques résistantes au traitement médical traditionnel. Contexte : Depuis près d’un siècle, le Mg a été utilisé en prophylaxie et dans le traitement des convulsions associées à l’éclampsie. L’effet du Mg sur le SNC est un effet dépresseur et il a également plusieurs fonctions à l’intérieur et à l’extérieur de la cellule. Cependant, le Mg a été peu évalué comme anticonvulsivant à cause de la disponibilité de médicaments dont l’efficacité est déjà bien établie. Méthode : Nous avons révisé rétrospectivement les dossiers de 22 patients atteints d’épilepsie réfractaire au traitement médicamenteux qui ont été traités de façon empirique par un supplément oral de Mg (surtout sous forme d’oxyde de Mg). Résultats : La prise d’un supplément de Mg par voie orale était associée à une diminution significative du nombre mensuel des crises, soit de 15.3 ± 13.2 (moyenne ± ET) à 10.2 ± 12.6 à la première visite de suivi après 3 à 6 mois de traitement (p = 0.021) et à 7.8 ± 10.0 crises par mois au moment de la deuxième visite de suivi après 6 à 12 mois de traitement (p = 0.004). Trente-six pour cent des patients avaient un taux de réponse de 75% ou plus au moment de la deuxième visite de suivi. Deux patients ont rapporté qu’ils n’avaient plus de crises. La plupart des patients étaient stables sous MgO 420 mg deux fois par jour ou, chez deux patients, sous lactate de Mg, sans effets indésirables importants le plus fréquent étant la diarrhée (4/22). Discussion : Selon ces résultats, la supplémentation orale en Mg peut s’avérer utile comme médicament d’appoint dans le traitement de l’épilepsie réfractaire au traitement médical. Conclusion : Il serait pertinent d’évaluer par une étude prospective, à double insu, contrôlée par placebo, le potentiel du Mg dans le traitement des crises résistantes au traitement médicamenteux.

The definitive treatment of eclampsia, a syndrome of pregnancy-induced hypertension, proteinuria and new onset seizures, is magnesium (Mg) supplementation, followed by delivery of the fetus. Magnesium has been the widely accepted treatment since first reported in 1925, and remains the mainstay of treatment for eclampsia. Eclamptic seizures have been compared, both in semiology and electrographically, to generalized tonic-clonic (GTC) “grand mal” seizures, with controlled clinical trials having demonstrated the clear effectiveness of Mg against eclamptic seizures when compared to conventional anticonvulsants.

Magnesium has been hypothesized to be effective against CNS ischemia and seizures based on its biochemical properties. Magnesium is a known CNS depressant, whose mechanisms of action include: competitive antagonism of N-methyl-D-aspartate (NMDA) receptors, blocking transient receptor potential (TRP) cation channels, antagonism of calcium channels (and subsequently, synaptic transmission) and increasing membrane surface charge which in turn decreases excitability.

To date, several studies have explored the use of Mg in ameliorating CNS pathology, however, clinical trials have failed to deliver on the promise of the effectiveness of Mg in animal...
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Adverse drug event reported was diarrhea, reported by four patients, three of which were on the MgO three times a day regimen. Two of these patients were switched to Mg-lactate, and subsequently reported increased gastrointestinal tolerability.

Twenty-seven percent (6/22) had a primary seizure disorder (generalized tonic clonic [GTC] or drop attacks) with the remaining 73% (16/22) having partial seizures (complex-partial seizures [CPS] – many of whom had secondary generalization, or simple partial). While Mg seemed more effective at increasing seizure free days/month (i.e. decreasing seizures) amongst the primary epilepsies, sub-group analysis via two-way repeated measures ANOVA comparing the effectiveness of Mg supplementation on primary generalized versus partial seizures revealed no statistical difference (p > 0.05).

Responder rates at first follow-up were as follows: 32% (7/22) had a reduction of 75% or greater in the number of seizure days per month, while 41% (9/22) had a reduction of 50% or greater in the number of seizure days per month. At second follow-up, both the 75% and 50% responder rates were 5/14 (36%), suggesting that the efficacy of MgO on seizures may be bimodal i.e. there may be a group of responders and non-responders. Of those who qualified as responders, 3/5 were classified as GTC, one with CPS and one with CPS with secondary generalization. Examination of the anti-seizure drugs did not reveal any obvious trends. This group of five patients were on an average of 2.8 ± 0.8 anti-epileptic medications, the most common being lamotrigine phenytoin, topiramate and valproate, all shared by two patients in the group. Four of the five were on a regimen of MgO twice a day dosing, compared to 68% of the cohort (15/22) who were on a regimen of MgO twice or more per day. Two of the 22 patients (9%) achieved seizure freedom.

Serum Mg levels were not drawn as a part of monitoring oral Mg therapy, however, several patients had serum Mg levels drawn as a part of routine in-patient hospitalizations. Eight patients had pre-treatment serum Mg levels drawn and four patients had post-Mg treatment levels drawn. All levels were within the normal range.

Discussion

Magnesium has been widely used by the obstetrics community for years in the treatment of eclampsia. Other clinical applications of Mg supplementation include ICU protocols, torsades ventricular arrhythmias, parathyroid syndromes, end-stage renal disease, insulin resistance and cardiovascular disease. While toxicity may manifest with respiratory depression and death, most common adverse events are diarrhea and hyporeflexia. Clinical signs of Mg imbalance often do not correlate with serum levels, as less than 1% is found in serum, with the bulk found in bone or intracellularly, where it acts as an important biochemical mediator. While serum levels were measured in the present study, Mg levels were all normal both before and after Mg supplementation. Reports have shown that seizure patients have lower ionized Mg²⁺, and higher ionized Ca²⁺/Mg²⁺ ratios, however, Mg levels do not correlate with seizure probability in the treatment of eclampsia.

Notwithstanding its wide spread clinical use and relatively benign adverse effects, Mg has not been tried for the treatment of patients established epileptic seizures, with the exception of its reported efficacy against infantile spasms as adjunctive
therapy with ACTH. It is widely accepted that a low Mg perfusion of in vitro brain preparations will readily generate seizures. However, animal research on the anti-seizure efficacy of Mg is equivocal. No effect of Mg was reported against amygdala kindling threshold in the rat. It also decreases seizures associated with intracranial NMDA injection when maximal electroconvulsive shock (MES) and pentylenetetrazol (PTZ) models of seizures are used. However, animal research on the anti-seizure efficacy of Mg is equivocal. No effect of Mg was reported against amygdala kindling threshold in the rat. It also decreases seizures associated with intracranial NMDA injection when maximal electroconvulsive shock (MES) and pentylenetetrazol (PTZ) models of seizures are used. However, animal research on the anti-seizure efficacy of Mg is equivocal. No effect of Mg was reported against amygdala kindling threshold in the rat. 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A randomized clinical trial investigating the neuroprotective effects of continuous Mg infusion in patients with traumatic brain injury did not demonstrate any positive benefits, yet Mg has been successful in the treatment of convulsions associated with porphyria. Intravenous Mg has been used in the past to successfully treat status epilepticus associated with Alper’s Syndrome, a triad of developmental delay, intractable seizures and hepatic failure.

Our patient population represents seizure patients who are the most difficult to treat medically. Nevertheless, Mg supplementation was able to significantly decrease the amount of seizure days/month, with two patients reportedly becoming seizure-free. However, there are multiple shortcomings which limit the ability to extrapolate these data. Firstly, this study was an open label, uncontrolled empiric study of the efficacy of Mg in a small population of patients with drug resistant seizures.
heterogeneous medical histories and reported anti-seizure drug regimens.

Secondly, MgO, one of the most affordable preparations, was used by most patients. However, its limited bioavailability, well-documented in the literature, is similar to other commonly used Mg compounds. Magnesium supplementation by mouth may be absorbed throughout the entire length of the small intestine, however, the bulk is associated with uptake in the distal jejunum and ileum, mainly by a passive intercellular process. Increased bioavailability of organic Mg compounds, such as Mg-Acetate, Mg-Lactate and Mg-Gluconate have been documented using both radio-isotopes and urinary Mg concentrations, and would be a better preparation for oral Mg delivery in future studies.

Similarly, the ability of Mg to penetrate the blood brain barrier in therapy-relevant concentrations has been the subject of some debate [see REF 5 for review]. Using MgCl₂, Oppelt et al. (1963) concluded that Mg uptake into the brain was an active process, keeping CSF concentrations greater than serum concentrations, and this was not affected by increasing Mg concentrations 3-4 fold. Similarly, Sun and colleagues (2009) found no increase in CSF Mg when MgSO₄ was injected intraperitoneally, in mice.

And yet, several studies have noted increased CSF Mg when supplemented parenterally, including pre-eclamptic patients and neurological patients undergoing ventriculostomy drainage or cranectomies. Similarly, rats injected intraperitoneally with MgSO₄ had significantly elevated CSF Mg levels at four hours, which coincided with elevated hippocampal seizure thresholds.

In all studies, including those where CSF Mg did not significantly increase, a significant rise in serum Mg was noted. However, when Mg levels were measured in this study as part of routine inpatient hospitalization, levels were all within normal limits. The usefulness of Mg levels prepared by the clinical laboratory is questionable, given that 99% of magnesium is intracellular [bone (53%); soft tissues (46%)] with 1% in the blood. Of the 1%, only the free ionized form is capable of transport across the blood brain barrier.

Future studies should include a blinded, placebo controlled protocol, with appropriate long term follow up, using organic Mg preparations such as Mg-Acetate, lactate or gluconate, and should coincide with monitoring of CSF Mg in attempt to correlate Mg levels with anti-seizure effectiveness. Monitoring intracellular red blood cell magnesium is another possible assay which may correlate with a decrease in seizures, and less invasive than obtaining CSF.

Standard anti-seizure medications are known for their wide adverse side-effect profile, whereas the adverse effects associated with Mg supplementation, which is quite inexpensive, are relatively benign and easily monitored. Given these data, clinical trials of the efficacy of Mg supplementation to routine anti-seizure therapy in medically responsive epilepsy are warranted.

REFERENCES