American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 11 (November), 2013: pp 1341-1348
Available online at www.jpain.org and www.sciencedirect.com

An Explanatory Study Evaluating the Muscle Relaxant Effects of Intramuscular Magnesium Sulphate for Dystonia in Complex Regional Pain Syndrome

Anton A. van der Plas, Johanna C. M. Schilder, Johan Marinus, and Jacobus J. van Hilten
Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.

Abstract: **The treatment of dystonia related to complex regional pain syndrome (CRPS) remains unsatisfactory, raising the need of alternative targets for intervention. In dystonia, pathologic muscle changes may occur, which contributes to stiffness. Because magnesium sulphate may act as a muscle relaxant through its actions on the neuromuscular junction and muscle, we performed an explanatory study of the muscle relaxant effect and safety of intramuscular magnesium sulphate (IMMG) in CRPS patients with dystonia. In a double-blind randomized placebo-controlled crossover study, 30 patients were assigned to 3-week treatments of IMMG and placebo. Treatments were separated by a 1-week washout period. The daily dose of IMMG was 1,000 mg in week 1, 1,500 mg in week 2, and 2,000 mg in week 3. The primary outcome measure was the difference in change in Burke-Fahn-Marsden scores after 3 weeks of treatment between both interventions. Secondary outcomes involved severity of dystonia, myoclonus, tremor, and pain, and functional activity. Data of 22 patients available for the explanatory analysis revealed no significant differences between IMMG and placebo treatment in any of the outcomes. In conclusion, we found no indication of efficacy of IMMG in a daily dose of 2,000 mg as a muscle relaxant in CRPS-related dystonia.**

Perspective: ***In this double-blind placebo-controlled crossover study there was no evidence found of a muscle relaxant effect of intramuscular magnesium sulphate in dystonia related to CRPS. Consequently, there is insufficient support for new studies evaluating the efficacy of other routes of MG administration in CRPS-related dystonia.***

Key words: *Intramuscular, magnesium sulphate, dystonia, complex regional pain syndrome.*

Complex regional pain syndrome (CRPS) is characterized by various combinations of sensory, autonomic, and motor disturbances, and its onset is usually triggered by trauma to a limb.[18] Dystonic postures are one of the most prevalent motor disturbances in CRPS, occurring in 20% of the patients.[8,10,33,44,46] Because these postures are frequently associated with severe disability,[3,44] several therapeutic efforts have been undertaken to correct or improve these postural abnormalities.[22,42,43,45] Systematic reviews on these efforts, however, have revealed a lack of evidence of symptomatic benefit of splints, oral muscle relaxants, and botulinum toxin A in CRPS-related dystonia.[28] Supported by findings from neurophysiological studies, which have highlighted the role of central disinhibition in this type of dystonia,[32,34,41] several studies have examined the efficacy of intrathecal baclofen.[42,43,45] Although this treatment may substantially decrease dystonia severity, the adverse event profile of this approach in CRPS is poor, and in 30% of cases no benefit was established.[45] Given the current status of treatment options for dystonia in CRPS, alternative targets for intervention are needed.

Apart from the central mechanisms involved in dystonia and spasticity, pathologic changes may occur in muscle tissue and this may contribute to stiffness such that the range of motion around a joint is limited.[36] Consequently, drugs that effectively reduce the influence of this factor may contribute to the treatment of dystonia in CRPS.

The regulation of muscle contraction is highly dependent on calcium fluxes in muscle tissue and at the

Received January 28, 2013; Revised May 24, 2013; Accepted May 29, 2013.
This study is part of TREND (Trauma RElated Neuronal Dysfunction), a Dutch Consortium that integrates research on epidemiology, assessment technology, pharmacotherapeutics, biomarkers and genetics on Complex Regional Pain Syndrome type 1. TREND is supported by a grant of the Dutch Ministry of Economic Affairs (BSIK03016).
J.J.v.H. has been a consultant for Medtronic and has received an unconditional research grant from Medtronic. He reports no financial interest on the subject matter or any competing materials.
A.A.v.d.P., J.C.M.S., and J.M. report no conflicts of interest.
Address reprint requests to Anton A. van der Plas, MD, Department of Neurology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. E-mail: A.A.van_der_Plas@lumc.nl
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.05.013

neuromuscular junction.[25,40] In turn, these calcium fluxes are controlled by magnesium,[7,15,21,26,47,48,50] which is demonstrated by the relaxant property of parenterally administered magnesium sulphate (MG) in both smooth and striated muscle.[17,29,31,39] Oral administration of magnesium salts, which are currently used in clinical practice, are not suitable for achieving efficient muscle relaxation because the systemic bioavailability of these salts is generally poor.[6,30] Although most studies used intravenous regimens to evaluate the effect of MG, intramuscular injections of MG (IMMG) proved equally effective in studies on (pre)eclampsia and severe head injury using similar dose regimens.[1,11,49] Additionally, in our experience, intramuscular injections may be preferred because CRPS patients are more susceptible to phlebitis during intravenous drug infusion.

This explanatory study was carried out to evaluate if there is supporting evidence of the muscle relaxant effects of IMMG in patients with CRPS-related dystonia, which would justify exploration of alternative modes of administration.

Methods

Patients

Subjects were male or female outpatients aged 18 years or older and diagnosed with CRPS-related dystonia. Patients had to fulfill the diagnostic criteria for CRPS I established at the Orlando consensus conference in 1993, which were the criteria formally endorsed by the International Association for the Study of Pain at the time this study started,[20] and to suffer from tonic or intermittent dystonia resulting in slight disability or worse in 1 or more extremities for at least 1 year. Patients were excluded in case of satisfactory relief of symptoms with conventional treatments or intrathecal baclofen. Other exclusion criteria were a history of alcohol or drug abuse within the past year, a clinically significant psychiatric illness, pregnancy, breastfeeding, childbearing potential without using effective contraception, a history of poor compliance to medical regimens or study requirements or the suspicion of poor compliance, insufficient command and understanding of the Dutch language, involvement in legal proceedings (claiming compensation for CRPS I), impaired coagulation or renal function (ie, serum creatinine below 10 or exceeding 80 μmol/L), hypermagnesemia (ie, total serum magnesium exceeding 1.10 mmol/L), or requirement of diuretics. The study lasted from October 2009 to May 2012. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethics Committee of the Leiden University Medical Center.

Study Design

This was a randomized placebo-controlled crossover study conducted at the movement disorders outpatient clinic of the Leiden University Medical Center. Patients, treating physicians, and assessors were blinded for the sequence of treatments.

An independent pharmacist randomized patients over the 2 sequences of IMMG and placebo in blocks of 4 using a computer-generated randomization list. Each subject received 2 intramuscular treatments of 3 weeks each: MG 100 mg/mL solution and sodium chloride .9% (placebo). Both treatments were separated by a 1-week wash-out period, which was considered sufficient based on the pharmacokinetic data on MG.[16] Patients self-administered intramuscular solutions twice per day during each treatment period. Treatment started at a daily volume of 5 mL twice a day and was increased in weeks 2 and 3 to twice-daily volumes of 7.5 and 10 mL, respectively. Syringes with .4-mm-diameter needles were used for infusion. Solutions were injected in the buttocks and the lateral upper margins of both thighs in alternating sequence. Intramuscular injections of MG can be painful and potentially contribute to unblinding. To alleviate the pain of intramuscular injections and reduce the risk of unblinding, 2.5 gram of lidocaine-prilocaine 5% cream (EMLA; AstraZeneca, Wilmington, DE) was applied 120 minutes before injection at the site of puncture. After application of the cream, the area was covered with a transparent film (Tegaderm; 3M Corporation, St. Paul, MN) prior to needle insertion to facilitate penetration through the various layers of the skin. This regimen has proved effective in decreasing both the superficial pain of needle puncture and the deeper pain of infiltration.[4,12,14,37] Prior to the first injection, patients were instructed how to prepare and perform the injections properly. If needed—because of the occurrence of (probable) severe or serious adverse events or the development of hypermagnesemia (ie, total serum magnesium level exceeding 1.10 mmol/L)—IMMG was reduced to the previous dose or stopped. In case of (probable) severe or serious adverse events, concentrations of free magnesium were measured. An independent data-monitoring committee reviewed unblinded data for patient safety. An investigator (A.A.v.d.P.) not involved in the clinical assessment of patients was exclusively informed on the presence of adverse events, the decision taken by the data monitoring committee, and the development of hypermagnesemia. Assessments were performed by another investigator (J.C.M.S.), who was blinded to these data and the allocated sequence of treatment. The study was registered in the Netherlands National Trial Register, number NTR 1873.

Outcome Measures

Patients were assessed 1 week before the first treatment was initiated and during both treatment regimens at days 1, 8, 15, and 22 prior to dose adjustment. Assessments were performed 2 hours after the first of the 2 daily injections of study medication. The efficacy assessments of movement disorders included the Burke-Fahn-Marsden (BFM) Dystonia Rating Scale,[5] the Barry-Albright Dystonia Scale,[2] the Unified Myoclonus Rating Scale,[9] and the Tremor Research Group Rating Scale.[13] The primary outcome measure was the difference in change of the BFM score over 3 weeks between IMMG and placebo. On the same days safety measurements were performed, including medical history taking, physical and neurologic examination, a 12-lead