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MAGNESIUM TOCOLYSIS

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In This Issue...

In 1995, it was thought that $MgSO_4$, in addition to being used as a tocolytic, could function as a prophylactic to lower the prevalence of neonatal IVH, infant mortality, and cerebral palsy. Unfortunately, as was discovered in the Magnesium and Neurologic Endpoints Trial (MagNET), high dose $MgSO_4$ appears to be associated with increased IVH and total pediatric mortality. However, because MagNET was suspended by the Institutional Review Board at the University of Chicago, a possible protective role for $MgSO_4$, as it pertains to cerebral palsy, remains unresolved.

In this issue – in a slight departure from our usual format – we present a discussion of neuroadverse outcomes following high dose exposure to $MgSO_4$, possible neuroprotective effects following low dose $MgSO_4$ exposure, and the evidence basis for the tocolytics that may replace $MgSO_4$.

THIS ISSUE

- **IN THIS ISSUE**
- **APRIL PODCAST**
- **COMMENTARY** from our Guest Editor

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- ALTERNATIVE TOCOLYTICS

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At the conclusion of this activity, participants should be able to:

- Identify the cranial ultrasound lesions in newborns that appear to be associated with high dose exposures to antenatal magnesium sulfate ($MgSO_4$)
- Discuss how low dose exposures to antenatal $MgSO_4$ may be associated with a neuroprotective effect in the developing infant and child
- Identify suitable tocolytics that can be used as replacements for $MgSO_4$

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COMMENTARY

In 1995, there was great interest, in both Chicago and Bethesda, to conduct a randomized study to find out whether magnesium sulfate ($MgSO_4$) could be used during preterm labor as a preventive for cerebral palsy. The intellectual basis for such a trial was a previously-conducted, very persuasive, case-control study[1]. Indeed, at the time, it seemed easy to test the 'magnesium hypothesis' because $MgSO_4$ was already being used commonly in the U.S. as a tocolytic. Moreover, it was being used successfully, and with good evidence basis, in maternal preeclampsia [2,3]. Indeed, despite the issues discussed herein, $MgSO_4$ remains the drug of choice for eclamptic seizure prophylaxis.

Thus, based on what was thought to be a solid epidemiologic foundation, the Magnesium and Neurologic Endpoints Trial (MagNET) was begun at the University of Chicago. The protocol was written by a collaborative group who convened at the National Institutes of Health, and the study was funded by the United Cerebral Palsy Research and Educational Foundation. Unfortunately, and to the disappointment of all involved, the trial was suspended after 15 months. Data analysis revealed a remarkable excess in total pediatric mortality (fetal + neonatal + postneonatal) among babies whose mothers had been randomized to $MgSO_4$. Including all data - $MgSO_4$ vs. other tocolytics (nifedipine, indomethacin, ritodrine, or terbutaline) or saline control - there were ten deaths in the $MgSO_4$ arms, whereas only one baby died in the other arms (Risk Difference, 10.7%, 95% Confidence Interval [CI] 2.9 to 18.5%; P=.02). At the request of the CP Foundation, these adverse events were published in Lancet in 1997[4]. As an aside, it should be noted that in the years following MagNET, it has been shown convincingly that $MgSO_4$ is ineffective as a tocolytic[5,6]. More importantly, in 2003, researchers from the Cochrane Database of Systematic Reviews confirmed the original findings from the MagNET Trial - that tocolytic $MgSO_4$ is associated with an increase in total pediatric mortality[7].

Moreover, in subsequent analyses of biological data from MagNET, additional evidence was found to support its original findings. Namely, a dose-response was found to exist between umbilical cord serum ionized magnesium levels at delivery and subsequent deaths in children — naturally, such a finding is important to help establish causation[8]. In addition, because cranial ultrasounds were done on all surviving babies, it was possible to study relationships between magnesium and brain abnormalities such as neonatal IVH, as well as a curious lesion in the

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thalami known as lenticulostriate vasculopathy (LSV). It was found in MagNET that higher maternal serum magnesium levels at delivery were related to neonatal IVH; IVH was found to be associated with LSV; and, to close the triangle, LSV was found to be associated with high exposures ($\geq$50 g) to tocolytic $MgSO_4$[9]. Naturally, this finding assumed importance as the biological consequences associated with the brain lesions could, at least partially, account for the observed increases in pediatric mortality.

As reviewed herein, there is evidence that is consistent with possible neuroprotective effects for $MgSO_4$ when used in low or modest doses, as well as reports (from MagNET) regarding adverse neurological outcomes associated with high dose magnesium exposures. Further, since any evidence-based plan to abandon $MgSO_4$ as a tocolytic requires substituting other, more effective drugs (if, in fact, tocolytics should be used at all in some circumstances), we discuss the efficacy of possible alternatives - specifically, nifedipine, beta-adrenergics, indomethacin, and nitroglycerin.

References

1. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? Pediatrics 1995;95:263-9.
2. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995;333:201-5.
3. Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995;345:1455-63.
4. Mittendorf R, Covert R, Boman J, Khoshnood B, Lee KS, Siegler M Is tocolytic magnesium sulphate associated with increased total paediatric mortality? Lancet 1997;350:1517-8.
5. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. Obstet Gynecol 1999;94:869-77.
6. Higby K, Suiter CR. A risk-benefit assessment of therapies for premature labor. Drug Saf 1999;21:35-56.
7. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev, March, 2003.
8. Mittendorf R, Covert R, Elin R, Pryde PG, Khoshnood B, Lee K-S. Umbilical cord serum ionized magnesium level and total pediatric mortality. Obstet Gynecol 2001;98:75-8.
9. Mittendorf R, Dammann O, Lee K-s. Brain lesions in newborns exposed to high dose magnesium sulfate during preterm labor. J Perinatol 2006;26:57-63.

NEUROLOGICAL EFFECTS & OUTCOMES

Crowther CA, Hiller JE, Doyle LW, Haslam RR. **Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial.** JAMA 2003; 290:2669-76.

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Mittendorf R, Dambrosia J, Dammann O, Pryde PG, Lee K-S, Ben-Ami TE, Yousefzadeh D. **Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage.** J Pediatr 2002;140:540-6.

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In 2003, the results of the Australasian Collaborative Trial of Magnesium Sulphate (ACTO$MgSO_4$), conducted by Crowther et al, was published in JAMA. It had been a randomized study designed to find out whether antenatal exposure to low

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dose (28 g or less) $MgSO_4$ in women at risk of preterm birth (<30 weeks gestation) could prevent subsequent pediatric mortality and cerebral palsy in their children. Australia and New Zealand were ideal for conducting a study such as ACTO$MgSO_4$ because magnesium is not used as a tocolytic in either of those countries. Thus, there was no ethical dilemma[1]in randomizing mothers to low dose $MgSO_4$ as a possible neuroprophylactic versus a saline control.

In ACTO$MgSO_4$, data analysis included a total of 1,047 preterm newborns (PN) who had been followed up to 24 months of age. It was found that administration of intravenous magnesium to a mother for 24 hours prior to birth significantly reduced a secondary outcome of the study, namely, subsequent gross motor dysfunction in her child (3.4% vs. 6.6%, Relative Risk [RR] 0.51; 95% CI, 0.29 to 0.91); further, it reduced death or substantial gross motor dysfunction (17.0% vs. 22.7%; RR 0.75, 95% CI 0.59 to 0.96) when considered as a secondary composite variable (death + motor dysfunction). However, for the prevention of cerebral palsy, the primary outcome of the study, the difference between the $MgSO_4$ exposed group and the placebo group was small and not significant (6.8% vs. 8.2%, respectively, P=0.38). Furthermore, differences between the magnesium group and the placebo group were not significant for other neonatal outcomes such as IVH, periventricular leukomalacia (PVL), chronic lung disease, necrotizing enterocolitis (NEC), or length of hospital stay in the NICU.

The important point is that ACTO$MgSO_4$ was a preventive trial – not a tocolytic trial – in which relatively low doses of magnesium were used. Indeed, although the research protocol for the study called for a 28 g exposure to $MgSO_4$, in practice, because of the inherent limitations in giving drugs to actively contracting women who might deliver at any time, including a time that preceded the receipt of a full course of $MgSO_4$, the actual median exposure to $MgSO_4$ was less than 10.5 g in the prophylactic magnesium arm of the study[2]. Of relevance in the U.S., when $MgSO_4$ is used as a tocolytic, the combined amount of the bolus dose (usually 4 to 6 g) plus the maintenance infusions (usually 2 or 3 g per hour) is considerably higher (the total amount often exceeding 50 g) than the prophylactic amounts used in ACTO$MgSO_4$.

As discussed in the 2002 article by Mittendorf et al, the unexpected and contrary reports about certain biological and adverse cranial ultrasound data from the Magnesium and Neurologic Endpoints Trial (MagNET) seem, on the surface, to be at variance with the benign and somewhat encouraging Australian findings. Originally, MagNET was designed to find out whether IV $MgSO_4$ given to women in preterm labor could do the following: a) prevent neonatal IVH, b) prevent excess deaths in PN (less than 34 weeks gestational age), and c) prevent the subsequent development of cerebral palsy. As it turned out, opposite to one of the primary intents of the trial, instead of decreasing the occurrence of neonatal IVH, PN whose mothers had high blood serum ionized magnesium levels at delivery were found to be at ***increased*** risk for IVH (adjusted [adj] Odds Ratio [OR], 15.8; 95% CI, 1.4 to 175.0).

To add further controversy to the role that high dose exposures to tocolytic $MgSO_4$ (50 g or more) may play in the development of neonatal brain abnormalities, as opposed to the possible neuroprotective benefits suggested in ACTO$MgSO_4$, an otherwise rare lesion of the thalami, lenticulostriate vasculopathy (LSV), was commonly found among MagNET babies[3]. LSV is a mineralizing vasculopathy affecting the striate arteries of the thalami (perforating branches of the middle cerebral arteries). Previously, although LSV had been found in congenital infections (most notably a rubella epidemic occurring in Philadelphia in the early 1960s), it had not been reported in association with high dosage exposures to magnesium. However, in MagNET, 14 cases of LSV were found and confirmed by independent cranial ultrasound review (Boston Children's Hospital and the Floating Hospital at New England Medical Center) in a cohort of

140 preemies. In a multivariate logistic regression that controlled for confounding, the relationship between antenatal exposure to high dose tocolytic $MgSO_4$ and the outcome of LSV was found to be significant (adj OR, 8.3; 95% CI, 1.3 to 45.0, P=0.01). Given that white matter injuries are common in PN, but those in the gray matter are not, it is fascinating that high dose $MgSO_4$ could be associated with lesions in the gray matter (thalami). Although the importance of any neurological morbidy that may be related to LSV remain in dispute, babies with LSV who have a readily identifiable underlying condition appear to have a high risk for long-term neuropsychiatric limitation[4].

In summation, a precise and comprehensive delineation of the effects of maternal magnesium exposure on the brain of the fetus, especially in regard to evaluating differences between low and high dose $MgSO_4$ exposures, needs to be done. Indeed, the relationships among a multitude of variables that may interact with magnesium (for example, antenatal corticosteroids and the various inflammatory cytokines) need additional study. Although the use of antenatal $MgSO_4$ for neuroprotection, even in very low doses, cannot be confidently recommended at the moment, it is possible that such will be so in the future. The findings of one study larger than ACTO$MgSO_4$, the Beneficial Effects of Antenatal Magnesium [BEAM] trial (Maternal-Fetal Medicine Network, National Institute of Child Health and Human Development), have not yet been reported. However, published data are consistent with an increased occurrence of neurological injury when exposures to antenatal $MgSO_4$ are at high levels. Fortunately, for the sake of children everywhere, much of this controversy is likely to be resolved over the course of the next several years.

References

1. Muraskas J, Marshal PA, Tomich P, Myers TF, Gianopoulos JG, Thomasma DC. Neonatal viability in the 1990's: held hostage by technology. Cambridge Quarterly of Healthcare Ethics 1999;8:160-72.
2. Mittendorf R, Lee K-S, Roizen NJ, Pryde PG. Magnesium sulfate for preterm neuroprotection. (Letter to the Editor.) JAMA 2004;291:940-1.
3. Mittendorf R, Kuban K, Pryde PG, Gianopoulos J, Yousefzadeh D. Antenatal risk factors associated with the development of lenticulostriate vasculopathy (LSV) in neonates. J Perinatol 2005;25:101-7.
4. Wang HS, Kuo MF. Sonographic lenticulostriate vasculopathy in infancy with tic and other neuropsychiatric disorders developed after 7 to 9 years of follow-up. Brain Dev 2003;25 Suppl 1:S43-7.

ALTERNATIVE TOCOLYTICS

Papatsonis DNM, van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. **Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial.** Obstet Gynecol 1997;90:230-4.

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Tsatsaris V, Papatsonis D, Goffinet F, Dekker G, Carbonne B. **Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis.** Obstet Gynecol 2001; 97:840-7.

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Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R (for the Canadian Preterm Labour Nitroglycerin Trial Group). **Randomized double-blind placebo-controlled trial**

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of transdermal nitroglycerin for preterm labor. Am J Obstet Gynecol 2007;196:37.e1-37.e8.

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If the use of magnesium sulfate ($MgSO_4$) is to be limited, or even eliminated, as a first-line tocolytic, then what agents are we to substitute, and what is the evidence basis for selecting alternative tocolytics among the drugs that are currently available for that purpose?

Among the drugs that are used for tocolysis in the U.S., ritodrine is the only one to ever receive approval by the Food and Drug Administration (FDA). However, despite that approval, it has been shown that beta-adrenergics, such as ritodrine and terbutaline (in common usage), are of limited effectiveness in prolonging pregnancy. Moreover, as a class of tocolytics, the beta-adrenergics, especially when used parenterally, pose a significant cardiovascular risk for the mother. Pulmonary edema, cardiomyopathy and even maternal death have all been shown to be associated with the use of these drugs. In the fetus, chronic use of beta-adrenergics has also been shown to have effects on glucose metabolism and cardiac function. Thus, when using this class of drugs, the clinician must proceed with utmost caution; however, in all fairness, the same warning applies to the use of any tocolytic, even the best among them.

Of importance, another class of tocolytics, the calcium channel blockers (potent anti-hypertensives), have been shown to be effective for tocolysis with less maternal and fetal toxicity than that seen with beta-adrenergics. Nifedipine, the prime example, has been well studied. Because it does not have an FDA approval for tocolyis, however, a relevant question would be: How favorably does nifedipine compare to the approved drug, ritodrine (and perhaps other beta-adrenergics) in regard to tocolytic efficacy and maternal and fetal safety? In 1997, Papatsonis et al directly compared nifedipine to ritodrine for tocolytic effectiveness. In a multicenter, randomized clinical trial, nifedipine was shown to significantly lengthen the interval from drug exposure to delivery at 24 hours (P=0.006), at 48 hours (P=0.03), at one week (P=0.009), and at 2 weeks (P=0.005). Concerning the neonate, there were no significant differences between nifedipine and ritodrine in regard to Apgar scores and umbilical cord pHs. Further, the nifedipine group had fewer admissions to the NICU (68% vs. 82%, P=0.04).

More recently (2001), Tsatsaris et al performed a meta-analysis of randomized clinical trials comparing nifedipine with the general class of beta-adrenergics, including ritodrine and other drugs (mostly terbutaline and salbutamol). Eleven published and two unpublished trials were included in the study. All were analyzed using intent-to-treat methodology. The meta-analysis showed that nifedipine was more effective than beta-adrenergics in delaying delivery for at least 48 hours (OR 1.52, 95% CI 1.03 to 2.24). Moreover, nifedipine was more effective in postponing delivery beyond 34 weeks of gestation (OR 1.87, 95% CI 1.11 to 3.15). For the neonate, a smaller percentage in the nifedipine group was transferred to the NICU (OR 0.65, 95% CI 0.43 to 0.97), and there were fewer cases of respiratory distress syndrome (RDS) (OR 0.57, 95% CI 0.37 to 0.89). There were, however, no significant differences in neonatal mortality between the two groups. In regard to the mother, nifedipine had substantially fewer maternal side effects than did the beta-adrenergics (OR 0.12, 95% CI 0.05 to 0.29). Of importance in clinical practice, when considering the use of nifedipine as a tocolytic, it is paramount to ensure there is no history of maternal cardiac disease or diabetes, and that sufficient intravenous hydration always precedes the administration of the drug.

Although the medical literature will not be reviewed here because they are secondary agents, other possible alternatives to tocolytic $MgSO_4$ include the

prostaglandin synthetase inhibitors and non-steroidal anti-inflammatory agents (NSAIDS). Of these, indomethacin has been shown to be effective. However, concerns regarding premature closure in the fetus of an otherwise patent ductus arteriosus, as well as concerns about reduction in renal arterial blood flow leading to oligohydramnios, limit its usage in clinical practice to short courses in women having preterm labor at less than completed 32 weeks. Also, recent analyses from observational studies have implicated the use of indomethacin with subsequent neonatal IVH and NEC. In their review of the subject, Macones at al(1) discussed concerns about methodological and confounding issues in studies linking indomethacin to IVH. In their conclusion, the authors opined that indomethacin was effective as a tocolytic, but due to potential risks, its use should be limited. In practical terms, indomethacin may serve as a useful adjunct tocolytic for short courses in women who are not eligible for other drugs. However, when using indomethacin, it is important to carefully monitor amniotic fluid volume with follow-up antepartum ultrasound examinations.

Of interest, the recently published Canadian trial by Smith at al has shown that transdermal nitroglycerin may prove to be an effective tocolytic. In a double-blind, placebo-controlled study, patients between 24 and 32 weeks gestation were randomized to either transdermal nitroglycerin (glycerol trinitrate, GTN) by patch or a look-alike placebo. When excluding patients who delivered at term, GTN-exposed pregnancies gained, on average, 10.8 days in gestational length as compared to control (P=.02). In the sub-group of women in preterm labor who were randomized at less than 28 weeks (and excluding those who ultimately had term deliveries), pregnancies were found to last, on average, 23.4 days longer (P=.007). Women receiving GTN did have more headaches. Analyzing neonatal outcomes as a composite variable (including chronic lung disease, IVH, NEC and PVL), those exposed to GTN had improved outcomes (RR 0.29, 95% CI 0.08 to 1.00, P=.048). It was suggested by the authors that this improvement was based on the substantial prolongation (23.4 days) of GTN-exposed pregnancies. Although these initial findings are encouraging, more investigation with this agent needs to be done in order to establish it as a superior tocolytic having a low risk profile. Especially needed is long-term pediatric follow-up.

In the future, it is conceivable that tocolytics with an enhanced biochemical specificity, such as oxytocin receptor antagonists, may be used successfully and safely. One such drug, atosiban, is currently being used in Europe and South America with some apparent success. However, in this country, the FDA did not approve the one commercially available oxytocin receptor antagonist because of an excess of unexplained neonatal deaths in its randomized trial(2). Of interest, in a recent meta-analysis comparing atosiban with nifedipine, Coomarasamy et al(3) found that atosiban was not superior to the calcium channel blocker in prolonging pregnancy beyond 48 hours. Moreover, nifedipine was found to reduce the prevalence of neonatal RDS (OR 0.55, 95% CI 0.32 to 0.97).

In conclusion, based on this review of the relevant evidence-based medical literature (with representative and additional articles being especially selected), it is concluded that nifedipine has the most support for use as a first-line tocolytic to replace $MgSO_4$. Although currently ongoing research may alter any future recommendation, extant data demonstrate the superior efficacy and improved safety profile of nifedipine as compared to other drugs currently being used in the United States for tocolysis.

References

1. Macones GA, Marder SJ, Clothier B, Stamilio DM. The controversy surrounding indomethacin for tocolysis. Am J Obstet Gynecol 2001;184:264-72.
2. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, Perry KG, Varner M, Goodwin TM, Lane R, Smith J, Shangold G, Creasy GW. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol 2000;182:1173-83.

3. Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour: a meta-analysis with an indirect comparison of randomised trials. BJOG 2003;110:1045-9.

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- Identify suitable tocolytics that can be used as replacements for $MgSO_4$

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