Magnesium for Preeclampsia and Eclampsia edit

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Medline Citation Magnesium was first used more than 60 years ago as a therapy for and prophylaxis against eclamptic seizures.1 It became standard treatment over the next 30 years and was associated with a dramatic reduction in maternal and neonatal morbidity related to **eclampsia**.2 Whether magnesium was responsible for the better outcome, however, was never tested in a randomized trial. Although newer and more effective anticonvulsant agents have become available, magnesium remains the mainstay of therapy for **eclampsia**. Its use has been criticized as being irrational, since it is not an anticonvulsant3 and is probably ineffective. On the other hand, it has been defended by obstetricians "because it works" and because the drug is safe for the fetus at therapeutically effective doses.4 New data demonstrate that magnesium is effective as both therapy for and prophylaxis against **eclampsia**, that it is indeed a rational form of therapy, and that it is not only safe for the neonate but also potentially beneficial.

In their article in this issue of the *Journal,* Lucas and coworkers convincingly demonstrate that, when administered to pregnant women with a presumptive diagnosis of pre**eclampsia** (a blood pressure exceeding 140/90 mm Hg), magnesium was far superior to phenytoin in preventing eclamptic seizures.5 The results seem conclusive. The two study groups were similar, and serum phenytoin concentrations were in the therapeutic range in the phenytoin group. The findings of this study are complemented by another recent randomized trial6 comparing the effectiveness of magnesium with that of diazepam and phenytoin to prevent recurrent seizures in women with established **eclampsia**. The **Eclampsia** Trial Collaborative Group reported that women receiving magnesium were half as likely to have recurrent seizures as women receiving diazepam and one third as likely as women receiving phenytoin.6 As in the study by Lucas et al.,5 the occurrence of seizures was associated with substantially increased maternal morbidity.

The argument that magnesium is safe for neonates is supported by both studies. Neonatal outcomes were virtually identical in the two treatment groups in the study by Lucas et al. In the Collaborative **Eclampsia** Trial, admission to an intensive care unit was more common among the infants of mothers who received phenytoin or diazepam, and status at birth, as indicated by Apgar scores, was worse. The potential benefit of magnesium to the neonate may extend even further. Nelson and Grether recently used a case–control approach to examine the risk of cerebral palsy in premature infants according to whether the mothers received magnesium during labor.7 They found an odds ratio of 0.14 (95 percent confidence interval, 0.05 to 0.51) for infants exposed to magnesium as compared with matched infants who were not exposed.7 Treatment was beneficial to the infants of mothers who received magnesium either for pre**eclampsia** or as treatment for preterm labor.

Several years ago the use of magnesium for pre**eclampsia** was deemed more a "religious conviction than a scientifically established treatment."3 The new studies5,6,7 now indicate that it actually has substantial beneficial effects in pre**eclampsia** and potential benefits for the neonate. It is quite likely that, independently of any anticonvulsant efficacy, magnesium has a myriad of other potentially beneficial actions. Although the cause of seizures in **eclampsia** has not been definitively established, pre**eclampsia** and **eclampsia** are characterized by intense vasospasm and increased sensitivity to pressors.8 This has led to the proposal that seizures are a response to reduced blood flow to the brain. Magnesium is a potent vasodilator, especially in the cerebral vasculature, and the administration of magnesium to women with pre**eclampsia** increases brain blood flow.9

Vasospasm in pre**eclampsia** is thought to be the consequence of endothelial dysfunction.8 Magnesium, both in vivo and in vitro, increases the production of the endothelial vasodilator prostacyclin.10 In addition, endothelial dysfunction is believed to be due to injury mediated by free radicals.8 Magnesium protects against such injury to endothelial cells in vitro.11 Magnesium may also protect against ischemic damage by substituting for calcium and preventing the entry of calcium ions into ischemic cells. The magnesium ion is also a cofactor for a multitude of enzymes, including many associated with energy metabolism. Finally, magnesium may be an anticonvulsant. It acts competitively to antagonize the glutamate *N*-methyl-D-aspartate receptor, which is epileptogenic.12

Magnesium should now be considered as a rational agent for the prevention and treatment of eclamptic seizures. The Collaborative **Eclampsia** Trial indicates that it is the drug of choice for treating eclamptic seizures, and the study by Lucas et al. shows that it is also the drug of choice for prophylaxis. An important question is, Who should receive prophylactic therapy?

The indication for therapy in the study by Lucas et al. was a blood pressure of more than 140/90 mm Hg during labor. An approach based on this criterion would result in the treatment of many women with preeclampsia who would not actually have seizures. Preeclampsia is not simply pregnancy-induced hypertension. It is likely that high blood pressure is important primarily as a marker for a panoply of other pathophysiologic changes in women with preeclampsia.[8] Epidemiologic studies indicate that there is a subgroup of women whose blood pressure rises late in pregnancy but who do not have the other pathophysiologic changes typical of preeclampsia. These mothers and their infants are not at increased risk for seizures or other adverse outcomes.[13] However, this subgroup of women can be identified only in retrospect, and consequently, any woman whose blood pressure increases during pregnancy should be considered to have preeclampsia. It would be useful if other findings in preeclampsia, such as proteinuria or central nervous system symptoms, could be used reliably to predict an increased risk of seizures. Unfortunately, this is not the case. For example, one study found that 20 percent of women with seizures did not have proteinuria.[14] On the basis of this finding, many advocate the approach described by Lucas et al.: treating all women with increased blood pressure. This treatment may be appropriate in the population studied by Lucas et al., consisting primarily of young black women, but it may not be appropriate in other populations. It seems likely that the risk of seizures varies in different populations.[5,15]

Eclampsia is still potentially fatal, and prevention would seem to be the most effective strategy. However, even among pregnant women with documented hypertension, the risk of having a seizure is very low.[15] Consequently, a strategy of treating all pregnant hypertensive women with magnesium sulfate would result in substantial overtreatment. Until better methods allow us to identify a higher-risk group for prophylactic treatment, this decision must unfortunately remain a matter of "religious"[3] or, in more contemporary terms, clinical conviction.

Another practical issue is the method of administration of magnesium. Lucas et al. used an intramuscular preparation. This regimen has been replaced in most centers by the less painful intravenous route. The blood levels achieved with the two regimens are equivalent, and no difference between the two was evident in the Collaborative Eclampsia Trial, in which both routes of administration were used. It seems reasonable to extend the conclusions of Lucas et al. to the intravenous regimen.

The studies by Lucas et al.,[5] the Eclampsia Trial Collaborative Group,[6] and Nelson and Grether[7] have important implications for reducing death and morbidity in mothers and their babies. They also demonstrate that an eclamptic seizure differs from other seizures, again indicating that preeclampsia is not just hypertension during pregnancy.[8]

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