International Journal of Obstetric Anesthesia (2005) **14**, 32–36

doi:10.1016/j.ijoa.2004.07.008

ORIGINAL ARTICLE

Magnesium and bupivacaine-induced convulsions in awake pregnant rats

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Background: Magnesium sulfate ($MgSO_4$) is widely used for the treatment and prevention of convulsions associated with preeclampsia. The aim of this study was to determine whether it alters the dose of bupivacaine required to produce convulsions in awake pregnant rats.

Method: Twelve pregnant rats were pretreated with an intravenous infusion of either $MgSO_4$ or saline. Following 2 h of the pretreatment, bupivacaine was concomitantly infused in all animals until the onset of convulsions. Mean arterial pressure (MAP) and heart rate (HR) were monitored throughout. Serial arterial samples were obtained during the infusion. At the onset of convulsions, fetuses were delivered and maternal and fetal blood, as well as various tissue samples, were obtained. All samples were assayed for bupivacaine and magnesium concentrations.

Results: Maternal MAP and HR decreased significantly shortly after the initiation of $MgSO_4$, while saline did not affect these measurements. Baseline concentrations of magnesium in plasma were similar in both $MgSO_4$ and saline groups; magnesium increased significantly during the infusion of $MgSO_4$. The dose (mean ± SD) of bupivacaine required to produce convulsions in the animals receiving $MgSO_4$ was significantly larger (10.2 ± 1.9 mg/kg) than that in the saline group (5.9 ± 1.0 mg/kg) ($P < 0.05$). As a consequence, bupivacaine concentrations in the brain and liver at the onset of convulsions were greater in animals receiving $MgSO_4$ (16.0 ± 8.4 and 18.2 ± 4.3 μg/g wet weight, respectively) than in those given saline (12.1 ± 2.2 and 9.9 ± 2.0 μg/g wet weight, respectively). Fetal bupivacaine concentrations at the onset of convulsions in the $MgSO_4$ group were also higher than those in saline group. However, the rate of placental transfer of this drug was similar between $MgSO_4$ and saline animals.

Conclusion: This study demonstrates that the clinically used concentration of magnesium sulfate increased the threshold of bupivacaine-induced convulsions in awake rats.

Keywords: Magnesium sulfate; Bupivacaine; Seizures; Rodent

INTRODUCTION

Magnesium sulfate ($MgSO_4$) has been widely used in obstetric practice for the treatment and prevention of convulsions associated with preeclampsia, as well as the primary application for preterm labor or pregnancy-induced hypertension.[1,2] Central nervous system (CNS) toxicity of local anesthetics is thought to be the result of a blockade of inhibitory pathways in the CNS.[3] Therefore, it is possible that the suppressive effect of magnesium on the CNS may inhibit local anesthetic-induced convulsions. In contrast to our assumption, previous investigators reported that magnesium sulfate did not suppress lidocaine-induced seizures in anesthetized rats.[4,5] Based on previous reports that nitrous oxide,[6,7] volatile[8] or intravenous[9,10] anesthetics affected the threshold of local anesthetic-induced seizures, we postulated that the suppressive effect of magnesium sulfate on the local anesthetic-induced seizures might be different if the animal was not anesthetized. Since bupivacaine is a commonly used local anesthetic in current obstetric practice, we chose this drug to test our hypothesis.

Accepted July 2004

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This work was supported in part by NIH grants R01 DA06648 and MHCRC30906.

METHODS

The experimental protocol was approved by the Columbia University Animal Care and Use Committee. Twelve near-term pregnant Sprague-Dawley rats weighing 330-400 g were obtained from a commercial breeder (CAMM, Ridgefield, NJ). They were housed in a temperature-controlled room on a 12-h light-dark cycle, and were given food and water ad libitum. The procedure for our chronically prepared rat model has been described elsewhere.[11] Briefly, under ketamine (40 mg/kg) and xylazine (7 mg/kg) anesthesia, a carotid artery and jugular as well as femoral veins were catheterized. The animal was then allowed to recover from anesthesia and surgery for at least 24 h. On the day of experiment, the rat was weighed and enclosed in a semi-dark observation box to observe the its behavior. An arterial catheter was connected to a transducer and Gould polygraph recorder (Model 30-V7404-00, Gould Inc., Cleveland, Ohio), which was connected to a DELL computer (OptiPlex Gs, Model DCM) in order to continuously monitor arterial blood pressure. Heart rate (HR) was obtained based on the beat-to-beat interval, derived from the pulse pressure curve. The animal was observed for at least 30 min before the experiment. Rats were randomly divided into two groups; six animals ($MgSO_4$ group) received a single intravenous bolus dose (50 mg/kg) of $MgSO_4$ (Abbott Laboratories, North Chicago, IL) in 5% $MgSO_4$ solution over a period of 2 min, which was followed by continuous infusion at a rate of 5 $mg{\cdot}kg^{-1}min^{-1}$ throughout the experiment. The remaining 6 animals (saline group) were given an equal volume of saline. After 2 h of infusion of either $MgSO_4$ or saline, all animals were concomitantly infused 0.5% bupivacaine HCl (AstraZeneca, Sweden) at the rate of 1 $mg{\cdot}kg^{-1}min^{-1}$ via a femoral vein until the onset of convulsions. One author (TO or YZ) was blinded to the infusate. Serial arterial blood samples (<0.5 mL each for one determination) were withdrawn for the measurement of magnesium and bupivacaine concentrations in plasma. Each sample was replaced by an equal volume of saline. For magnesium concentration, the baseline sample was obtained before $MgSO_4$ or saline infusion and in the $MgSO_4$ group additional samples were withdrawn at 1 and 2 h during the infusion. At the onset of convulsions, a blood sample was taken from all animals. The animals were then placed in a beaker containing a gauze sponge saturated with isoflurane. As soon as the animals became unconscious (within 5-7 s), the heart was removed to stop the circulation, and the brain was removed. The uterine horns were exteriorized, all blood vessels supplying the uterus were clamped, and a fetal blood sample was obtained by cardiac puncture, then the fetal brain was removed. Maternal and fetal liver were also obtained. All blood samples were centrifuged and plasma was separated and stored at −70°C until analyzed.

Magnesium concentration in the plasma was analyzed by the colorimetric endpoint method based on the fact that magnesium forms a colored complex with magon dye (xylidyl blue-1) in a strong alkaline solution. The reagents used were obtained from DMA (Data Medical Associates, Inc., Arlington, TX). The absorbance of the complex was measured spectrophotometrically at 520 nm. Concentrations of bupivacaine in plasma and tissues were analyzed by liquid chromatography with spectrophotometric (Ultraviolet) detection, based on a procedure by Kastrissios et al.[12] with modifications.[13] A detection limit of 0.5 ng/mL for bupivacaine was obtained.

Differences between all chronological variables within the group were tested using repeated measures analysis of variance (ANOVA), with Fisher PLSD tests used for post hoc comparisons. Differences between the groups were tested using unpaired t tests. Values are expressed as mean ± SD, and a P value of 0.05 was considered significant. All analyses were done using StatView Version 5 (Abacus Concepts Inc., Berkeley, CA).

RESULTS

Mean (± SD) values for mean arterial blood pressure (MAP) and heart rate at baseline, after the 2-h infusion of $MgSO_4$ or saline and at the onset of convulsions are listed in Table 1. Following $MgSO_4$ infusion, MAP and HR decreased significantly ($P < 0.05$) from baseline, while the values remained essentially unchanged in the saline group. During bupivacaine infusion, MAP gradually increased ($P < 0.05$) and HR decreased ($P < 0.05$), followed by generalized tonic and clonic convulsions. Magnesium concentrations in the plasma before and during infusion of either $MgSO_4$ or saline are listed in Table 2. The baseline values were similar in the two groups. Following infusion of $MgSO_4$, plasma values increased significantly, while the values in the saline group remained unchanged.

The dose of bupivacaine required to produce convulsions in the $MgSO_4$ group (10.2 ± 1.9 mg/kg) was significantly greater ($P < 0.05$) than in the saline group (5.9 ± 1.0 mg/kg). The duration of bupivacaine infusion necessary to produce convulsions in animals receiving $MgSO_4$ (10.2 ± 1.9 min) was therefore significantly greater ($P < 0.05$) than in those receiving saline (5.9 ± 1.0 min). Bupivacaine concentrations in plasma and tissue at the onset of convulsions are summarized in Table 3. All plasma and tissue concentrations of bupivacaine in the mother and fetus were higher in the $MgSO_4$ group, as a result of receiving a greater dose of bupivacaine. Fetal to maternal bupivacaine concentration