Magnesium Sulfate Potentiates Several Cardiovascular and Metabolic Actions of Terbutaline*


β-Adrenergic agonists are useful for the emergency treatment of asthma. Recently, magnesium sulfate (MgSO₄) has also been shown to be efficacious in this situation. β-Agonists have unwanted cardiovascular and metabolic actions: increased systolic blood pressure, corrected QT interval (QT), serum glucose and insulin, and decreased RR interval, diastolic blood pressure, serum potassium, phosphate, and calcium. As β-agonists and MgSO₄ quite possibly will be used in combination, we sought to determine how MgSO₄ would affect these actions. Healthy young male adults were administered two doses of terbutaline sulfate, 0.25 mg subcutaneously, 30 min apart on two separate occasions, in a randomized, double-blind fashion. On one occasion, 4 g of MgSO₄ was administered intravenously over the same 30-min period. On the other, normal saline solution was given as a placebo. Cardiovascular and metabolic variables were measured sequentially for 2 h. Data at 60 min with p values given for a summation of all time points are as follows: MgSO₄ increased terbutaline’s effects on the RR interval by 0.09 s, p < 0.0001; QT interval by 0.01 s, p < 0.0007; diastolic blood pressure by 8 mm Hg, p = 0.0001; serum calcium by 0.13 mg/dl, p = 0.01; and glucose by 9 mg/dl, p < 0.0001. MgSO₄ also mitigated the systolic blood pressure elevating the effect of terbutaline by 5 mm Hg (p = 0.007). The magnitude of the response potentiations was modest. We conclude that combining terbutaline and MgSO₄ is unlikely to result in serious short-term adverse events, if used acutely in patients with relatively normal cardiac and metabolic function. MgSO₄ may act by potentiating the effects of β-agonists on magnesium requiring enzymes such as adenyl cyclase. (Chest 1994; 105: 701-05)

MgSO₄ = magnesium sulfate; QTₙ = corrected QT interval

Magnesium sulfate has been shown to have some efficacy in the treatment of asthma in the emergency department, a feature it shares with β-adrenergic agents. MgSO₄ appeared to be more effective in the study using it after a β-agonist then in the studies using it alone or vs a β-agonist in a matched group. MgSO₄ has also been used for the treatment of certain cardiac dysrhythmias, such as multifocal atrial tachycardia, supraventricular tachycardia, and torsades de pointes (polymorphous ventricular tachycardia). The latter dysrythmia is associated with pre-existing prolongation of the QT interval.

β-Adrenergic agents have unwanted cardiovascular and metabolic effects. They increase the heart rate and systolic blood pressure, decrease the diastolic blood pressure, and increase the corrected QT interval (QTₙ). The metabolic effects include decrease in serum potassium, calcium, and phosphate levels, and increase in the serum glucose and insulin levels. Intravenous magnesium also has notable cardiovascular and metabolic effects. It may increase cardiac output 20 to 35 percent and lower peripheral vascular resistance. Blood pressure may be lowered transiently but heart rate is not affected. The PR interval may be increased as may the QRS complex. The sinus node recovery time is increased and the atrioventricular conduction time and refractory period are also prolonged by intravenous magnesium sulfate. It also decreases serum ionized calcium and increases the serum potassium levels.

Since β-adrenergic agents and MgSO₄ are likely to be used in combination, we sought to determine the effect of MgSO₄ on the cardiovascular and metabolic actions of the β-adrenergic agent, terbutaline. Study of possible drug-drug interactions is particularly important as concern has been voiced that β-agonists may be toxic and may be contributing to increased morbidity and mortality from asthma.

METHODS

Eight healthy male volunteers, aged 24 to 29 years, were

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Table 1—Effect of Terbutaline With and Without MgSO₄ on Cardiovascular and Metabolic Variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline*</th>
<th>60 min</th>
<th>60 min</th>
<th>∆ 60-min</th>
<th>∆ 60-min</th>
<th>F₁</th>
<th>p₁</th>
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<tbody>
<tr>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
<td>Baseline</td>
<td>Baseline</td>
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</tr>
<tr>
<td></td>
<td>+MgSO₄</td>
<td>−MgSO₄</td>
<td>+MgSO₄</td>
<td>+MgSO₄</td>
<td>−MgSO₄</td>
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<tr>
<td>RR, s</td>
<td>0.93 (0.12)</td>
<td>0.69 (0.10)</td>
<td>0.75 (0.12)</td>
<td>−0.25 (0.13)</td>
<td>−0.16 (0.08)</td>
<td>21.8 &lt; 0.0001</td>
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<tr>
<td>QT, s</td>
<td>0.37 (0.02)</td>
<td>0.40 (0.03)</td>
<td>0.41 (0.04)</td>
<td>+0.03 (0.02)</td>
<td>+0.05 (0.03)</td>
<td>0.15 0.7</td>
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<tr>
<td>QTc, s</td>
<td>0.38 (0.02)</td>
<td>0.48 (0.04)</td>
<td>0.48 (0.04)</td>
<td>+0.10 (0.04)</td>
<td>+0.09 (0.04)</td>
<td>12.5 0.0007</td>
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<tr>
<td>BP, mm Hg</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>110 (9.8)</td>
<td>123 (9.3)</td>
<td>125 (8.7)</td>
<td>+12.5 (4.2)</td>
<td>+17 (8.6)</td>
<td>7.61 0.0071</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>72 (9.4)</td>
<td>51 (5.4)</td>
<td>51 (13.2)</td>
<td>−25.5 (8.5)</td>
<td>−17 (13.1)</td>
<td>17.8 0.0001</td>
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<tr>
<td>K⁺, mEq/L</td>
<td>4.2 (0.2)</td>
<td>3.4 (0.4)</td>
<td>3.5 (0.2)</td>
<td>−0.74 (0.26)</td>
<td>−0.75 (0.24)</td>
<td>0.165 0.69</td>
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<tr>
<td>Mg²⁺, mEq/L</td>
<td>1.5 (0.1)</td>
<td>3.0 (0.4)</td>
<td>1.5 (0.1)</td>
<td>+1.33 (0.31)</td>
<td>−0.05 (0.08)</td>
<td>80.3 &lt; 0.0001</td>
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<tr>
<td>PO₄⁻, mg/dl</td>
<td>3.4 (0.3)</td>
<td>2.6 (0.4)</td>
<td>2.8 (0.4)</td>
<td>−0.78 (0.25)</td>
<td>−0.64 (0.40)</td>
<td>3.0 0.09</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺, mm/dl</td>
<td>9.3 (0.2)</td>
<td>8.8 (0.2)</td>
<td>9.0 (0.2)</td>
<td>−0.50 (0.15)</td>
<td>−0.38 (0.28)</td>
<td>6.6 0.01</td>
<td></td>
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<tr>
<td>Glucose, mg/dl</td>
<td>85 (5.1)</td>
<td>122 (13.2)</td>
<td>112 (7.8)</td>
<td>+36.7 (11.4)</td>
<td>+27.9 (8.8)</td>
<td>34.4 &lt; 0.0001</td>
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<tr>
<td>Insulin, μU/ml</td>
<td>20.2 (3.2)</td>
<td>32.0 (4.3)</td>
<td>30.9 (7.8)</td>
<td>+12.3 (2.8)</td>
<td>+10.1 (5.0)</td>
<td>0.085 0.77</td>
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*Mean of baseline on both visits.

F₁ and p values represent the potentiation of terbutaline's effect by MgSO₄ over the entire period of observation.

MgSO₄ reduces terbutaline's effect on systolic blood pressure.

studied in a double-blind randomized crossover fashion. The study was approved by the hospital’s Human Studies Subcommittee. Informed consent was obtained from each subject before starting the study. Exclusion criteria were as follows: upper respiratory tract infection within 4 weeks, history of cigarette use, cardiopulmonary disease, or use of any medications. Subjects refrained from caffeine products for 24 h before each experiment. Each subject was studied twice; the studies were done 7 days apart. Each study was begun between 7:30 and 9 AM after an overnight fast. With the subjects in the supine position, two intravenous lines were placed, one for phlebotomy and one for drug infusion. On both visits the subjects received two doses of 0.25 mg of terbutaline sulfate subcutaneously 30 min apart. On one visit they received 4 g of MgSO₄ in 250 ml of normal saline solution intravenously over 30 min, beginning with the initial terbutaline dose. On the other visit, they received 250 ml of normal saline solution as a placebo. Placebo and MgSO₄ solutions were prepackaged by the pharmacy in identical vials, coded and distributed in a randomized fashion. Serial 1-min rhythm strips from lead II of the standard ECG were obtained for the measurement of RR and QT intervals. The QT interval was calculated in the standard fashion. Blood was drawn at baseline 15, 30, 45, 60, and 120 min, starting at the first terbutaline injection for later determination of serum potassium (ion selective electrode), magnesium (calmagite reaction), calcium (ion selective electrode), phosphate (phosphomolybdate reaction), glucose (hexokinase reaction), and insulin (radioimmunoassay) levels. Blood pressure (sphygmomanometry) and heart rate were also determined at the same intervals.

The significance of changes from baseline in electrolyte, glucose, and insulin levels, RR, QT, and QT intervals, and blood pressure were analyzed by three-way (subject, time, and presence or absence of MgSO₄) analysis of variance. The effect of terbutaline on serum magnesium on the placebo day was analyzed by paired Student's t test.

RESULTS

Baseline (mean of both days), 60-min data for both the MgSO₄ and the placebo days, and 60-min minus baseline data for both days are shown in Table 1. Terbutaline decreased the RR interval (F = 2.4, p < 0.04) and this effect was magnified by MgSO₄ (F = 21.8, p < 0.0001) (Fig 1). The mean decrease in RR interval at 60 min was 0.09 s greater with MgSO₄. The QT interval was not significantly increased by terbutaline (F = 2.6, p = 0.03). MgSO₄ likewise had no effect on this measure (F = 0.01, p = 0.70). On the other hand, the QT interval was increased by terbutaline (F = 6.4, p < 0.0001) and this effect was augmented by MgSO₄ (F = 12.5, p = 0.0007) (Fig 1). The mean increase in the QT interval at 60 min was 0.01 s greater with MgSO₄.

Systolic blood pressure was increased by terbutaline sulfate (F = 3.2, p = 0.01). This effect was lessened by MgSO₄ (F = 7.6, p = 0.007) (Fig 2), which attenuated the increase found with terbutaline by a mean of 5 mm Hg at 60 min. Terbutaline and MgSO₄ also had significant effects on the diastolic blood pressure. Terbutaline decreased this measurement dramatically (F = 6.7, p < 0.0001) and the addition of MgSO₄ lowered diastolic pressure even more (F = 17.8, p = 0.0001) (a mean of 8 mm Hg more at 60 min) (Fig 2). Terbutaline reduced serum potassium level (F = 26.2, p < 0.0001); MgSO₄ had no additive effect (F = 0.165, p = 0.69). Of course, MgSO₄ infusion increased serum magnesium level (F = 803, p < 0.0001) (mean maximal increase, 1.61 mEq/L at 30 min). Terbutaline did not significantly affect the serum magnesium level on the placebo day (1 h vs baseline magnesium: p > 0.25). Terbutaline caused the serum phosphate level to drop significantly (F = 7.4, p < 0.0001); MgSO₄ tended to increase this effect, but not to a statistically significant degree (F = 3.0, p = 0.09) (a mean of 0.14 mg/dl more at 60 min). Terbutaline lowered the serum calcium level (F = 5.0, p = 0.0005) and MgSO₄ augmented this effect (F = 6.6, p = 0.01) (a mean of 0.13 mg/dl more at 60 min) (Fig 3).

Terbutaline increased the serum glucose level (F = 24.6, p < 0.0001) and this effect was magnified.

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by MgSO₄ (F = 34.4, p < 0.0001) (a mean of 9 mg/dl more at 60 min). Terbutaline also increased insulin levels (F = 9.9, p < 0.0001); magnesium had no effect here (F = 0.085, p = 0.77). Thus, magnesium augments the hyperglycemic effects of terbutaline, though not by affecting the insulin level.

**DISCUSSION**

We found that MgSO₄ augments most, but not all, of the cardiovascular and metabolic actions of the β-adrenergic agonist terbutaline. The heart rate, QT, interval, diastolic blood pressure, and serum calcium and glucose effects of terbutaline were magnified by MgSO₄ infusion. A nonsignificant trend for magnesium to augment the effects of terbutaline was seen with serum phosphate. On the other hand, magnesium lessened the effect of terbutaline on systolic blood pressure. Magnesium did not significantly alter the effects of terbutaline on serum potassium and insulin levels. Thus, of the 11 items we measured, 7 (including serum magnesium) were altered by the administration of MgSO₄. The peak action of intravenously administered MgSO₄ is delayed, indicating that transfer to intracellular sites is required.²⁷,²⁸ Our results are consistent with this concept. Most of the effects we studied peaked at 60 min, 30 min after the infusion was completed. Serum calcium change leveled off at 90 min. By 120 min, most measures were returning toward baseline,
serum calcium being an exception.

In our study, no effect of terbutaline on serum magnesium levels was noted. Other work in this area has yielded varying findings. Epinephrine (β₁ and β₂-adrenergic agonist) lowered serum magnesium levels more than albuterol (β₂ specific). However, another study showed an initial small increase in the serum magnesium level with epinephrine. Other studies showed more pronounced decrements in serum magnesium levels with terbutaline (also β₂ specific), particularly after 2 h. These varying results may reflect differences in protocol as well as dissimilarities in the pharmacologic effects of these adrenergic agents.

Magnesium is an essential co-factor for more than 300 enzymes, including adenyl cyclase and sodium-potassium ATPase. β-Adrenergic agonists are capable of activating these two enzymes. Interestingly, both β-agonists and magnesium relax uterine smooth muscle and are used to treat preterm labor. Similarly, both agents used in our study have been reported to lower serum calcium levels. Thus, our findings that magnesium augments many β-adrenergic functions are not surprising.

That MgSO₄ is a more potent and long-acting bronchodilator if administered after a β-adrenergic agonist is consistent with our results. Perhaps magnesium acts in part by offsetting β-agonist tachyphylaxis. This cannot be determined by our study using healthy individuals naive to β-adrenergic agonists. Likewise, one cannot directly apply our results to patients with asthma and COPD. On the other hand, such patients would have widely varying β-agonist usage histories and also likely would have developed varying degrees of tolerance to them, making data regarding interaction with MgSO₄ difficult to interpret.

Can MgSO₄ increase the potential of β-agonists to cause cardiac or metabolic toxicity? In the healthy subjects we studied the degree of changes noted by adding magnesium was of a modest degree. The augmentation of the heart rate effect of terbutaline by magnesium is counterposed by a tendency of magnesium to mitigate the systolic blood pressure effect of terbutaline. Consequently, there were no significant differences between the two limbs of our study with regard to “double product” (systolic blood pressure times heart rate). Thus, it is unlikely that magnesium would significantly affect myocardial work and oxygen demand above and beyond the effects of terbutaline alone, to the extent that these are indicated by the double product.

On the other hand, the combination of magnesium with a β-agonist significantly lengthens the QT interval more than terbutaline alone. Thus, the combination may be more dysrhythmogenic than administration of a β-agonist alone. However, this is unlikely to be the case, as magnesium has antiarrhythmic effects, particularly in the prolonged QT syndromes, in the context of cardiac glycoside toxicity, following acute myocardial infarction (improving outcome in this condition), and after cardiac surgery. Nevertheless, clinicians should be aware of the possibility of dysrhythmia when prescribing the combination. The metabolic effects we found were of a modest degree. It is unlikely that they would result in serious adverse events in the short term. Though MgSO₄ potentiates several cardiovascular and metabolic effects of β-agonists in a healthy population, we found no serious contraindication to their concomitant use.

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