Magnesium sulphate as an alternative and safe treatment for severe persistent pulmonary hypertension of the newborn

J-F Tolsa, J Cotting, N Sekarski, M Payot, J-L Micheli, A Calame

Abstract

Eleven newborns admitted consecutively to the neonatal unit with respiratory failure and severe persistent pulmonary hypertension (PPHN) were included in a clinical trial to assess the efficacy of magnesium sulphate (MgSO₄) in the treatment of PPHN. A loading dose of 200 mg/kg MgSO₄ was given over 20 minutes, followed by a continuous infusion of 20–150 mg/kg/hour to obtain a magnesium blood concentration between 3.5 and 5.5 mmol/l. Mean (SD) duration of treatment was 75.5 (19.8) hours. No other vasodilatory drug was administered before or during the treatment and patients were not hyperventilated. Mean (SEM) PaO₂ values significantly increased from 42.6 (8.8) before treatment to 70.3 (24.1) mm Hg after 24 hours, with no change in pH or Pco₂. Oxygen index and alveolar-arterial oxygen gradient (A-aDo₂) were significantly lower after 24 hours; respectively, 46.8 (15.2) to 28.0 (9.0) and 624.3 (11.3) to 590 (58) mm Hg. Mean airway pressure could be significantly reduced from 19.5 (3-1) to 13.9 (3-9) cm H₂O after 72 hours. Mean ventilatory time support was 131 hours and mean total oxygen dependency 10 days. No systemic hypotension nor any other adverse effect were noted. All infants survived and the neurodevelopmental assessment was normal at 6 and 12 months of age.

It is concluded that magnesium sulphate is a non-aggressive and low-cost treatment of short duration which is easy to apply. It may have a role in the various treatment of PPHN.

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Keywords: persistent pulmonary hypertension, magnesium sulphate, newborn.

Methods

Eleven newborns admitted consecutively to the neonatal unit with respiratory failure and profound hypoxaemia due to severe persistent pulmonary hypertension were enrolled into the trial. The diagnosis of PPHN was considered when there was either a persistent hypoxaemia (PaO₂ of <50 mm Hg or 6.7 kPa) out of proportion to the degree of severity on the chest radiograph despite an adequate ventilatory support and/or an important lability of oxygenation with great variations in PaO₂ without changes in ventilator settings. Before inclusion all the infants either had an oxygen index above 40 (mean (SEM) 46.8 (15.2)) or an A-aDo₂ of ≥610 mm Hg (mean (SEM) 624.3 (11.3)); heart defects were excluded and pulmonary hypertension always confirmed by echocardiography. The clinical findings in these infants are shown in the table.

Four infants were inborn and seven outborn. There were four females and seven males. Gestational age ranged from 35 to 40 weeks (mean (SD) 36.7 (1.3) weeks) and birthweight from 2260 to 3570 g (mean (SD) 2956 (449) g). All were appropriate for gestational age and none of them presented with congenital malformations. Mean Apgar scores
Clinical findings in the patients studied

<table>
<thead>
<tr>
<th>Case No</th>
<th>Birthplace</th>
<th>Sex</th>
<th>Gestation (weeks)</th>
<th>Birthweight (g)</th>
<th>Primary diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Outborn</td>
<td>F</td>
<td>38</td>
<td>3160</td>
<td>AS, thrombocytopenia</td>
</tr>
<tr>
<td>2</td>
<td>Inborn</td>
<td>M</td>
<td>37</td>
<td>2970</td>
<td>AS</td>
</tr>
<tr>
<td>3</td>
<td>Outborn</td>
<td>M</td>
<td>37</td>
<td>1550</td>
<td>SBS, pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>Inborn</td>
<td>F</td>
<td>36</td>
<td>2830</td>
<td>AS</td>
</tr>
<tr>
<td>5</td>
<td>Inborn</td>
<td>F</td>
<td>36</td>
<td>2600</td>
<td>AS, neonatal hypocalcemia</td>
</tr>
<tr>
<td>6</td>
<td>Outborn</td>
<td>M</td>
<td>37</td>
<td>3570</td>
<td>HMD</td>
</tr>
<tr>
<td>7</td>
<td>Inborn</td>
<td>M</td>
<td>36</td>
<td>2900</td>
<td>AS</td>
</tr>
<tr>
<td>8</td>
<td>Outborn</td>
<td>F</td>
<td>35</td>
<td>2260</td>
<td>HMD</td>
</tr>
<tr>
<td>9</td>
<td>Inborn</td>
<td>M</td>
<td>36</td>
<td>2870</td>
<td>AS</td>
</tr>
<tr>
<td>10</td>
<td>Outborn</td>
<td>M</td>
<td>36</td>
<td>3500</td>
<td>Pneumonia, pneumothorax, thrombocytopenia</td>
</tr>
<tr>
<td>11</td>
<td>Outborn</td>
<td>M</td>
<td>40</td>
<td>3560</td>
<td>AS, perinatal asphyxia</td>
</tr>
</tbody>
</table>

AS: aspiration syndrome; HMD: hyaline membrane disease; SBS: Streptococcus B sepsis.

were 8:1 at one minute and 8:2 at five minutes. Only one term infant had perinatal asphyxia (Apgar 8/3/5). Seven infants presented with aspiration syndrome, two with hyaline membrane disease, one with pneumonia and one with Streptococcus B sepsis. Informed consent was obtained from all parents.

All patients were first given routine supportive treatment including: (1) haemodynamic support by volume expansion up to 20 to 30 ml/kg and, if necessary, with continuous dopamine infusion at 5 to 20 mg/kg/minute; (2) sedation with morphine infusion at 10 to 20 mg/kg/hour with additional doses of 0.1 mg/kg if necessary and; (3) appropriate ventilatory support (Bear Cub infant ventilator). Before and during MgSO4 treatment, heart rate, mean arterial blood pressure (MAP), temperature, and ventilator settings with inspired oxygen fraction (FiO2), respiratory rate, peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), and mean airway pressure (Paw) were recorded at two hour intervals during the first day of treatment and then from six to six times a day.

The blood gas measurements (pH, PaO2, Pco2) were obtained through an indwelling arterial umbilical catheter (Argyle 3-5 or 5-5 French guage) positioned at L3 to L4, and measured with an ABL 300 acid base laboratory analyser.

All the variables and results are expressed as mean±one standard deviation (SD). Before MgSO4 infusion was begun, all infants were ventilated with 100% FiO2 at a rate of 45-1 (15-7)/minute with high PIP of 35-9 (4-4) cm H2O and a PEEP of 3-5 (0-9) cm H2O. Mean airway pressure was 19-5 (3-1) cm H2O. Blood gas analysis showed a pH value of 7.34 (0.09) and a Pco2 of 45.1 (12.0) mm Hg. Hypoxaemia was confirmed with a PaO2 of 42.6 (8.8) mm Hg. In case 6 arterial PO2 could not be obtained before the start of treatment because of a technical difficulty. Severity of impairment of gas exchange was evaluated after oxygen index and A-aDO2 had been calculated according to the formulas: oxygen index=PaO2×FiO2/PaO2 and A-aDO2 (mm Hg)=760 ×FiO2−(PaO2+Pco2+47), where PaO2 (mm Hg) is the post-ductal arterial oxygen tension and Pco2 (mm Hg) the carbon dioxide tension. MgSO4 infusion was started at a postnatal age of 25.0 (12.2) hours (range 8.5–53 hours). Pancuronium was administered if the PIP was above 30 cm H2O and or if the patient's respiration was not synchronous with the ventilatory rate.

A loading dose of 200 mg/kg MgSO4 diluted to 10% in sterile water was given intravenously over 20 minutes, followed by a continuous infusion of 20 to 150 mg/kg/hour, to obtain a magnesium blood concentration between 3.5 and 5.5 mmol/l. Magnesium blood concentrations were monitored twice hourly within the first 24 hours and three to four times a day after stabilisation. No other vasodilatory drug was used before or during the treatment. The patients were not hyperventilated or alkalised.

Once the PaO2 was stabilised, ventilator settings were then reduced first by decreasing the pressures and then the FiO2. Pancuronium was usually stopped during the second day of treatment and patients ventilated in the prone position as soon as possible.

Multiple means were compared by analysis of variance followed by a t test using the Bonferroni correction if ANOVA showed significant treatment effects.21 Paired t tests were used to compare values before MgSO4 infusion and after 24, 48, and 72 hours of treatment. A p value of <0.05 was considered significant.

Results

The blood magnesium concentration in relation to treatment (in hours) is illustrated in fig 1. Magnesium blood concentrations increased rapidly during the first three hours of treatment to reach a mean (SD) value of 4.16 (0.99) mmol/l after six hours of treatment. With continuous infusion, the blood concentration was then kept between 3.5 and 5.5 mmol/l. Mean duration of treatment was 75 (19-8) hours with a range from 44 to 114. No important hypocalcaemia was noted and only a few infants received transiently a 10% calcium gluconate infusion.

The evolution of the PaO2 is shown in fig 2. In all infants PaO2 improved rapidly and increased from 42.6 (8.8) mm Hg before treatment to 70.9 (15.5) six hours later, and to 70.3 (24.1) after 24 hours of treatment (p<0.01). At 48 and 72 hours of treatment, PaO2 values remained significantly higher — respectively, 71.7 (15.2) mm Hg (p<0.001) and 81.5 (14.3) (p=0.001), at lower FiO2.
All infants survived, had a normal neurological examination, and normal head ultrasound scans at hospital discharge. Ten of the 11 infants were examined in the developmental unit between 6 and 12 months of age and all had a normal development. One child lives abroad and is normal according to his parents and paediatrician.

**Discussion**

The regulation of the pulmonary circulation before and after birth reflects a balance between factors producing active pulmonary vasoconstriction and vasodilation.22 Despite a better understanding of the underlying pathophysiology and the various treatments that have been proposed,23 pulmonary hypertension remains a potentially fatal complication among newborns.24 In the absence of specific pulmonary vasodilators, ECMO and other vasodilating agents given by inhalation have been used or are currently under investigation.25,26

At high serum concentrations, magnesium is a muscle relaxant, a sedative, and a potent vasodilatory drug. Its effects on the vascular system have been studied in animals.15,16 It is a modulator of vascular contraction and an activator of many cellular processes, including cation transport and modulation of membrane excitability, and it is a physiological calcium antagonist.11

MgSO₄ has already been given as rescue treatment to newborns with severe PPHN.18 In this study we used magnesium without any other vasodilatory agent or hyperalkalinisation. Our 11 patients all presented with a severe PPHN, evidenced by refractory hypoxaemia with a high oxygen index and A-aDO₂. After a loading dose of MgSO₄, the magnesium blood concentration of 3.5–5.5 mmol/l was rapidly obtained and easily maintained with a continuous infusion. During treatment, a rapid increase in PaO₂ was observed, allowing a progressive reduction in Paw and FiO₂, resulting in a decrease of severity indices. Furthermore, with these high magnesium blood concentrations, babies were more stable and had fewer PaO₂ fluctuations. This was probably due to the sedative and relaxing effects of magnesium. Nursing in the prone position was then possible, shortening the duration of ventilation and oxygen dependency that are usually required by these very sick neonates.

None of the known side effects of high dose magnesium was observed. The slight decrease in heart rate was easily corrected by dobutamine support. Blood pressure remained stable and increased progressively with postnatal age. Feeding was well tolerated.

Despite high indices of mortality, all infants survived. At discharge from hospital they all had normal neurological findings and normal brain ultrasonography. None of them developed chronic lung disease and at follow up all had normal development. Sensory hearing loss has been reported in infants with PPHN.27 This has not yet been detected in our patients.
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In conclusion, this report provides evidence that magnesium can play part in the treatment of persistent pulmonary hypertension of the newborn. It is a non-aggressive treatment of short-duration and low cost. Based on these encouraging results, all patients presenting to our unit with PPHN are currently receiving MgSO\textsubscript{4} as the first drug of choice in a prospective protocol. Clinical controlled studies in life threatening conditions, however, are difficult to perform. Nevertheless, comparison between different approaches in the treatment of PPHN is certainly necessary for the evaluation of their respective benefits.

Experimental studies of magnesium and its possible interactions with natural vasodilators, such as prostacyclins, nitric oxide, and the guanylate cyclase pathway, would be suitable areas to investigate in the future.


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