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Effects of magnesium sulphate and nitric oxide in pulmonary hypertension induced by hypoxia in newborn piglets

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Abstract

Aim—To examine the haemodynamic effects of intravenous magnesium sulphate on an animal model of neonatal pulmonary hypertension induced by hypoxia.

Methods—The cardiac index (Q), pulmonary arterial pressure (PAP), systemic arterial pressure (SAP), and pulmonary (PVRI) and systemic (SVRI) vascular resistance indices were measured in nine newborn piglets (including three controls). Pulmonary hypertension was induced by lowering the F_{IO_2} to 0.12–0.14, after which there was a significant increase in PAP and PVRI (37% and 142%, respectively; $p < 0.01$) and a significant fall in SAP and Q (30% and 33%, respectively; $p < 0.01$).

Results—Magnesium sulphate was infused intravenously as four doses of 25 mg/kg, 15 minutes apart, which resulted in a significant mean (SD) increase in serum magnesium (0.83 (0.07) mmol/l to 1.82 (0.19) mmol/l; $p < 0.01$). After the initial dose SAP, SVRI, PAP and PVRI decreased, but not significantly. Each subsequent dose of (50, 75, 100 mg/kg) was accompanied by further significant reductions in these variables from control baseline ($p < 0.05$). The PVRI:SVRI ratio remained unchanged throughout. Inhaled nitric oxide (NO) 40 ppm was administered after the last dose of magnesium sulphate. The PVRI:SVRI significantly decreased ($p < 0.05$), indicating that reversible pulmonary hypertension remained after a maximum dose of magnesium sulphate.

Conclusions—Unlike NO, magnesium sulphate is not a selective pulmonary

vasodilator and may lead to deleterious effects on systemic pressures in critically ill newborns.

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Persistent pulmonary hypertension of the newborn is characterised by high levels of pulmonary vascular resistance, resulting in right to left shunting across the ductus arteriosus and foramen ovale.^{1–3} The magnitude of this shunt depends on the ratio of the systemic and pulmonary vascular resistance. Vasodilators, such as nitrates, tolazoline, calcium channel blockers and others, have little potential for directly decreasing shunt across these fetal channels because of non-differential effects on both systemic and pulmonary vascular resistance.^{4–6}

Magnesium, which has been called nature's calcium blocker,⁷ antagonises calcium ion entry into smooth muscle cells, thereby promoting vasodilation.⁸ While it has also been proposed as a possible selective pulmonary vasodilator,⁹ magnesium sulphate infusion (200 mg/kg) produced a significant fall (34.6%) in mean pulmonary artery pressure (PAP), but also a 37.4% decrease in systemic arterial pressure (SAP) in an adult sheep model of pulmonary hypertension induced by hypoxia.¹⁰

Haemodynamic responses can vary considerably in a young animal compared with a mature animal. The aim of this study, therefore, was to examine the haemodynamic effects of magnesium sulphate at various doses in a newborn pig model of pulmonary hypertension induced by hypoxia and to compare these responses with those seen with the inhalation of nitric oxide (NO), a known selective pulmonary dilator.^{11–16}

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Methods

Nine newborn mixed breed piglets were studied. The surgical technique and experimental protocol were approved by the Animal Care Committee of the University of Alberta.

SURGICAL TECHNIQUE

General anaesthesia was induced with halothane 5% and maintained with oxygen (5 l/minute) and halothane 2%. An incision in the right side of the neck was performed and a catheter inserted through the external jugular vein and advanced to the right atrium to measure right atrial pressure (RAP). A catheter was inserted into the right carotid artery to measure continuously mean SAP. Halothane was discontinued and fentanyl 20 µg/kg and acepromazine 0.2 mg/kg, followed by a continuous infusion of fentanyl 10 µg/kg/hour, were given intravenously. A 3.0 mm endotracheal tube was inserted through a tracheostomy. Muscle relaxation was maintained by intravenous pancuronium bromide (100 µg/kg) every 45 minutes.

Ventilation of the neonate was initiated with a peak inspiratory pressure (PIP) of 12–14 cm H₂O, a positive end expiratory pressure (PEEP) of 2 cm H₂O, a rate of 35–40/minute and inspiratory time of 0.35 seconds (Sechrist IV 100B, Sechrist Industries, Anaheim, California). The FIO₂ was adjusted to maintain arterial oxygen saturation (SaO₂) of >95%. Arterial blood gas values were maintained at a pH of 7.35–7.45, a PCO₂ of 35–45 mm Hg, and a PO₂ of 60–80 mm Hg (IL Micro 13 pH/blood Gas Analyzer, Instrumentation Laboratories, Fisher Scientific, Lexington, Massachusetts) by appropriate ventilator adjustments. The SaO₂ was measured using a transcutaneous pulse oximeter (N200, Nellcor Inc, Hayward, California). Hydration during surgery was maintained with 30 ml/kg/hour of sodium bicarbonate (15 mEq/100 ml) in 5% dextrose to compensate for high insensible losses through the thoracotomy, and to prevent severe acidosis during the periods of hypoxia.

A 6 or 8 mm Transonic transit time ultrasound flow probe (Transonics Corporation, Ithaca, New York) inserted through a left thoracotomy was placed around the main pulmonary artery to measure cardiac output. A similar flow probe was placed around the ductus arteriosus. A 22 g catheter was inserted into the root of the pulmonary artery through a purse string suture to measure the PAP. Confirmation of catheter placement was made by identifying the characteristic wave forms. Arterial, atrial, and pulmonary artery catheters were connected to a pressure transducer (Hewlett Packard Model 1290A, Palo Alto, California), zeroed at the midcardiac level, and signals were recorded and displayed with a monitor (Model 78833B, Hewlett Packard, Waltham, Massachusetts). Body temperature was monitored continuously with a rectal probe connected to a Hewlett Packard monitor and maintained between 38 and 39°C using a heating pad.

DATA COLLECTION

Data were collected continuously in a 486 personal computer (Dell Inc, Richmond Hill, Ontario) via an analogue to a digital converter (DT2801, Data Translation Inc, Marlborough, Massachusetts), using the Asyst scientific software system (Macmillan Software Co, New York). All signals were acquired at 24 Hz and programs were written to create correctly configured files and to acquire, store, and analyse the data. Pulmonary vascular resistance index (mm Hg/(ml/kg/minute)) was calculated as the quotient of PAP and cardiac index (Q) and SVRI (mm Hg/(ml/kg/minute)) was calculated as the quotient of SAP minus RAP and Q.

MEDICATIONS

Magnesium sulphate heptahydrate (MgSO₄ 7H₂O; Abbott Laboratories) 50% solution was diluted to the equivalent of magnesium sulphate 25 mg/kg (equivalent to 0.1 mmol of elemental magnesium) per 2 cc physiological saline. Magnesium concentrations were measured by colorimetry (Ektachem; Kodak, Rochester, New York). Nitric oxide in nitrogen, in a concentration of 800 ppm (Canadian Liquid Air, Edmonton, Alberta), and containing less than 5 ppm of nitrogen dioxide, was introduced into the ventilator circuit after being passed through a barolime scrubber which, when dry, removes nitrogen dioxide but not NO. The concentration of NO downstream from the scrubber was controlled by a Matheson Kitagawa flowmeter (model 8014-400A) and was continuously measured using a chemiluminescence toxic gas analyser (Model 42H, Thermo Environmental Instruments Ind, Franklin, Massachusetts) which analyses NO concentrations (between 20 and 250 ppm), total oxides in nitrogen, and nitrogen dioxide by subtraction.

EXPERIMENTAL DESIGN

After instrumentation the animal was allowed to recover for 20 minutes or longer until there was less than 5% variation in the baseline heart rate, cardiac output, SAP, and PAPs and SaO₂. Hypoxia was then induced by reducing the inspired oxygen concentration (FIO₂=0.12–0.14) to a target PaO₂ of 25–30 mm Hg with an SaO₂ of 30–50%, resulting in pulmonary hypertension.¹⁷ Three of the animals were monitored for 30 minutes as controls and did not receive magnesium sulphate. In the remaining six animals haemodynamic measurements (SAP, heart rate, Q, PAP, RAP and ductal flow) were recorded for two minutes and a baseline magnesium sample (1 cc) was taken. Magnesium sulphate (25 mg/kg) was injected over one minute into the central venous catheter. Haemodynamic variables were recorded during and after the infusion. Stabilisation (defined as <5% variation in the haemodynamic variables) generally occurred within 10 minutes of administration of the drug. A two minute section of the record was marked for averaging after haemodynamic

Mean (SD) haemodynamic and blood gas variables during normoxia and following induction of hypoxia

	Normoxia	Hypoxia
RAP (mm Hg)	6 (2)	7 (3)
PAP (mm Hg)	27 (9)	37 (10)*
PVRI (mm Hg/(ml/min/kg))	0.09 (0.03)	0.22 (0.10)*
SAP (mm Hg)	67 (14)	47 (11)*
SVRI (mm Hg/(ml/min/kg))	0.24 (0.07)	0.26 (0.08)
Q (ml/min/kg)	292 (68)	192 (85)*
PaO ₂ (kPa)	13.0 (5.0)	3.1 (0.5)*
PACo ₂ (kPa)	5.1 (1.6)	5.2 (0.8)
pH	7.42 (0.11)	7.35 (0.11)

*Significant differences between means ($p < 0.001$).

stabilisation. Magnesium concentrations were taken from the arterial line before the next dose of the drug was administered. This procedure was repeated three times in each animal, resulting in the total administration of 100 mg/kg of magnesium sulphate.

Fifteen minutes later NO (40 ppm) was given via the inspiratory line of the ventilator while the animal was still hypoxic and a further set of haemodynamic measurements was obtained. The animals were then killed with intravenous pentobarbital (Wyeth Laboratories, Philadelphia).

STATISTICAL ANALYSIS

The results were expressed as means (SD) and comparisons were made using two way factor analysis of variance (ANOVA) without replication. The factors used in the ANOVA were the different animals and the phases (baseline, and magnesium sulphate at 25, 50, 75, 100 mg/kg, and NO at 40 ppm). When a significant F value ($p < 0.05$) was obtained, the means were compared using the post hoc test of Fisher's protected least significant difference.

Results

All nine piglets, aged 1–2 days, weighing 1.1–1.8 kg (mean (SD) 1.4 (0.3) kg), survived to complete the experiment. The normoxic and baseline control hypoxic variables are

Figure 1 SAP (open circles) and PAP (closed circles) decreased significantly from baseline hypoxia, after magnesium sulphate in doses of 50, 75, and 100 mg/kg. PAP, but not SAP, decreased significantly after NO 40 ppm ($p < 0.05$).

Figure 2 SVRI (open circles) and PVRI (closed circles) decreased significantly from baseline hypoxia, after magnesium sulphate in doses of 50, 75, and 100 mg/kg, while PVRI:SVRI (closed squares) remained unchanged. PVRI, but not SVRI, decreased significantly after NO 40 ppm ($p < 0.005$).

presented in the table. After hypoxia had been induced there was a significant increase in PAP and PVRI (37% and 142%; $p < 0.01$) and a significant fall in SAP and Q (30% and 33%; $p < 0.01$) while SVRI remained unchanged. There was no change in RAP.

Serum magnesium concentrations rose significantly from control baseline values of 0.83 (0.07) mmol/l to 1.82 (0.19) mmol/l following the administration of 100 mg/kg magnesium sulphate. Concentrations at 25, 50, and 75 mg/kg magnesium sulphate (1.17 (0.07), 1.34 (0.08), and 1.58 (0.16) mmol/l, respectively) were also significantly increased from control baseline value ($p < 0.05$). The three control animals had similar changes after hypoxia and had no significant changes in haemodynamic variables during the monitoring period.

Administration of the first two doses of magnesium sulphate (25 mg/kg twice) were associated with transient bradycardia which returned to baseline (245 (16) bpm) within 60 seconds. The third and fourth doses (75 and 100 mg/kg, cumulative) were associated with significant decreases in heart rate from baseline (232 (20) and 218 (28) beats per minute (bpm), respectively; $p < 0.01$). Although Q decreased from baseline (192 (63) ml/kg/minute) with each increment of magnesium sulphate (25, 50, 75, and 100 mg/kg), these differences were not significant (204 (60), 186 (48), 172 (45), and 166 (35) ml/kg/minute, respectively).

The infusion of magnesium sulphate was associated with a progressive decrease in SAP, PAP, SVRI and PVRI, which were significantly lower than control hypoxic baseline at 50, 75, and 100 mg/kg of magnesium sulphate ($p < 0.05$) (figs 1 and 2), but not with the initial dose (25 mg/kg). The PVRI:SVRI ratio did not change from baseline at any increment in magnesium sulphate, indicating that the falls in PVRI and SVRI were proportional (fig 2). There were no significant changes in RAP (6,

7, 5, and 7 mm Hg, at each 25 mg/kg increment in magnesium sulphate, respectively).

Despite the noticeable systemic and pulmonary hypotension after a dose of magnesium sulphate the administration of inhaled NO 40 ppm resulted in a significant decrease in PAP and PVRI without significant changes in SAP, SVRI, or RAP. There was also a significant decrease in PVRI:SVRI ratio after inhaled NO, indicating selective vasodilation of the pulmonary vasculature ($p < 0.05$) (fig 2). Oxygen saturation remained unchanged throughout the hypoxic portion of the study and ductal flow was not detected at any time during the study.

Discussion

The characteristics of an ideal pulmonary vasodilator include an ability to lower pulmonary vascular resistance without systemic vasodilation and to increase cardiac output, pulmonary blood flow, and oxygenation. The current study, using a neonatal animal model, indicates that magnesium sulphate showed none of these beneficial haemodynamic characteristics in a neonatal model of hypoxia induced pulmonary hypertension. Rather, the administration of incremental doses of magnesium sulphate (25 mg/kg) was associated with a consistent fall in PAP and PVRI proportionate to reductions in SAP and SVRI. Cardiac output actually decreased and there was no change in oxygen saturation. In contrast, inhaled NO, given after magnesium sulphate, was associated with a decrease in PAP and PVRI, without a change in SAP and SVRI. These data confirm that in this neonatal model of hypoxia induced pulmonary hypertension and in these doses magnesium sulphate is not a specific pulmonary vasodilator.

Although the ductus was not ligated, we did not detect any flow at any time during the study, indicating that the ductus was functionally closed in this neonatal model. Right to left shunting across the foramen ovale could not be excluded. Therefore, some underestimate of systemic blood flow and overestimate of SVRI may have occurred. This increase in systemic blood flow would have favoured a beneficial effect of magnesium sulphate on the PVRI:SVRI ratio, if magnesium sulphate was indeed a specific pulmonary vasodilator.

One explanation for the observed differences between neonatal and adult animal¹⁰ responses to magnesium sulphate may be known age dependent differences in cardiovascular responses to hypoxaemia. Although both neonatal and mature animal models show a rise in PVRI with hypoxia, the systemic responses to hypoxia are opposite.^{17,18} We observed a decrease in SAP and Q in neonatal piglets with acute hypoxaemia while others have shown an increase in these variables in more long term experiments.¹⁹ Neonatal lambs are unable to maintain stroke volume during acute hypoxaemia and show a fall in stroke volume when compared with the infant animal.¹⁸ The neonatal myocardium, being relatively deficient in sarcoplasmic reticulum,

is also more dependent on extracellular calcium for excitation-contraction coupling.²⁰ Thus neonatal cardiac function is extremely sensitive to hypocalcaemia and the negative inotropic effects of calcium channel blockers are more pronounced. This could also explain why neonatal piglets are more susceptible to the hypotensive effects of magnesium sulphate compared with adult sheep.

Our own clinical experience with magnesium sulphate in critically ill newborns is that it is often associated with deleterious effects on systemic blood pressure, even at relatively low infusion rates (50 mg/kg/hour). Indeed, magnesium sulphate has been used for decades as an antihypertensive agent, perhaps with most success in the treatment of toxemia of pregnancy where its sedative, anticonvulsant, and uterine relaxation properties have been particularly useful.²¹ The hypotensive actions of magnesium sulphate are related in part to its vasodilatory properties. However, increased magnesium concentrations have a direct negative inotropic effect on cardiac contractility and may also interfere with catecholamine action. In adult cardiac surgical patients magnesium significantly blunted the hypertensive action of epinephrine and prevented a significant increase in mean arterial pressure during concurrent magnesium sulphate-epinephrine administration.²² More recently, in a neonatal piglet model, magnesium has been shown to have a protective effect against epinephrine induced cardiotoxicity because of its blocking action on the calcium influx of ionised calcium.²³

After their observations on the effect of magnesium sulphate on a mature sheep model Abu-Osba *et al* treated 10 infants with persistent pulmonary hypertension with magnesium sulphate (bolus 200 mg/kg over 20–30 minutes, followed by an infusion of 20–50 mg/kg/hour).⁹ Arterial PO₂ increased, PaCO₂ decreased and there was a rise in arterial pH. Mean systemic blood pressure decreased from 54 to 47 mm Hg at two hours but returned to baseline values at eight hours. They suggested that the improvement in these infants may have resulted from a selective decrease in pulmonary vascular resistance and thus right to left shunt. The results of the present study suggest that a differential decrease in pulmonary vascular resistance in proportion to systemic vascular resistance is unlikely to account for their observations. Other potential effects of magnesium sulphate, including its sedative, muscle relaxant, and bronchodilator effects,^{24–26} may lead to an improvement in oxygenation and ventilation in certain circumstances.

In the present study the PVRI:SVRI ratio decreased only after administration of inhaled NO, indicating that NO is a truly selective pulmonary vasodilator in this model of pulmonary hypertension. NO was only administered at the completion of magnesium sulphate infusion, suggesting that magnesium sulphate does not completely reverse pulmonary hypertension induced by hypoxia. There is some suggestion that the action of magnesium on smooth

muscle contraction may be related to the formation or release of endothelium derived relaxing factor which is now known to be NO.²⁷ Nitric oxide binds to reduced haemoglobin, forming nitrosylhaemoglobin, and has an affinity for haemoglobin about 1500 times greater than that of carbon monoxide. Nitrosylhaemoglobin is then oxidised to methaemoglobin with the production of nitrite and nitrate, a process which is much faster and more complete in oxygenated blood. This rapid metabolism of NO accounts for the absence of systemic haemodynamic effects with inhaled NO. Nitric oxide has been shown to be a specific pulmonary vasodilator in animal models of pulmonary hypertension,^{16 28} in infants with persistent pulmonary hypertension,^{29–31} and in adults with adult respiratory distress syndrome.³²

There are many theoretical and clinically demonstrated beneficial effects of magnesium on the lungs in adults and mature animal models. Magnesium may protect adult lungs from oxygen toxicity³³ and it attenuates monocrotaline induced pulmonary hypertension and right ventricular hypertrophy in rats.³⁴ Hypomagnesaemia may be arrhythmogenic^{35 36} and may be associated with hypocalcaemia unresponsive to calcium supplementation.³⁷ Magnesium depletion (for example, by diuretics) should be avoided and hypomagnesaemia should be corrected by the addition of magnesium sulphate to replacement fluids. However, our results do not support a clinical role for the clinical use of moderate or high dose (50–200 mg/kg) magnesium sulphate infusions in infants with persistent pulmonary hypertension in whom maintenance of systemic arterial pressures is of critical importance. Rather, controlled trials of magnesium sulphate infusions in such infants, as suggested by others,⁹ should be approached with caution. Any potential role for magnesium sulphate in these circumstances will probably be superseded by inhaled NO, which has direct pulmonary vasodilator properties without adverse systemic haemodynamic effects.

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