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Effects of pretreatment with magnesium on muscle relaxation and cardiovascular responses in tracheal intubation using the priming principle for vecuronium

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Abstract: In addition to its direct effects on blood vessels, the myocardium, and neuromuscular junctions, magnesium can act as an adrenergic antagonist and can inhibit the release of catecholamines both from adrenergic nerve terminals and from the adrenal medulla. This study was undertaken to evaluate these effects of magnesium on muscle relaxation and cardiovascular response during tracheal intubation. Forty ASA I or II patients undergoing elective surgery were allocated to a magnesium or a control group. Three minutes after priming with vecuronium 0.015 mg·kg^{-1}, the magnesium group received vecuronium 0.085 mg·kg^{-1} and magnesium sulfate 40 mg·kg^{-1}, while the control group received an equivalent volume of vecuronium and saline. The percent change from baseline in mean arterial pressure after tracheal intubation was significantly smaller ($P < 0.01$) in the magnesium group than in the control group, but the percent change in heart rate was similar. There were no significant changes in plasma catecholamine concentrations after tracheal intubation in either group. The onset time of vecuronium was significantly shorter in the magnesium group than in the control group. The duration of action of vecuronium was significantly longer in the magnesium group than in the control group. Serum magnesium concentrations at 90 min after its administration were significantly higher than baseline. We concluded that vecuronium priming with magnesium pretreatment inhibits the hypertension associated with tracheal intubation and shortens the onset time of vecuronium, but prolongs it duration of action.

Key words: Priming principle, Vecuronium, Magnesium

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Introduction

Although nondepolarizing muscle relaxants lack the serious adverse effects of succinylcholine, at reasonable doses, their onset time is not short enough for use in early tracheal intubation. Furthermore, large doses of nondepolarizing muscle relaxants can cause undesirable cardiovascular and other adverse effects [1]. The vecuronium priming principle may be an alternative method for accomplishing early tracheal intubation without serious adverse effects. However, its onset time is still relatively slower than that of succcinylcholine [2].

Magnesium inhibits presynaptic acetylcholine release at the motor end plate and acts as a minor calcium antagonist on the muscle itself. As a result, magnesium has been reported to potentiate the effects of nondepolarizing muscle relaxants and conceivably, could shorten their onset time [3–6]. James et al. [7] compared magnesium sulfate pretreatment and the priming principle in pancuronium onset time, concluding that pretreatment with magnesium does not significantly accelerate the onset of action of pancuronium. The influence of magnesium on vecuronium onset time has not been studied.

Magnesium also has cardiovascular effects, acting both as a calcium antagonist and an adrenergic antagonist. As a result, magnesium acts both as a vasodilator and an antiarrhythmic agent [3–6,8,9]. Conceivably, with these dual effects, magnesium could attenuate the undesirable cardiovascular responses associated with tracheal intubation.

The purpose of this study was to evaluate the ability of magnesium to shorten vecuronium onset time and to inhibit undesirable cardiovascular responses and catecholamine release using the priming principle in tracheal intubation.

Materials and methods

This study was approved by our hospital ethics committee, and all patients gave their informed consent. Forty ASA I or II patients of both sexes, aged 19–70 years, were randomly allocated to one of two groups (magnesium and control group) with 20 patients in each group. None of the patients had renal dysfunction. All patients were premedicated with hydroxyzine 25 mg (≦50 kg) or 50 mg (>50 mg) and atropine 0.75 mg (≦50 kg) or 1.0 mg (>50 kg) orally 1 h prior to surgery. An intravenous infusion of lactated Ringer's solution was started before anesthetic induction. The left radial artery was cannulated for blood sampling.

Three minutes before the induction of anesthesia, the patients in both groups received a priming dose of vecuronium 0.015 mg·kg^{-1}. Anesthesia was induced with thiopental 5 mg·kg^{-1} and ventilated with 100% oxygen using a breathing mask until tracheal intubation. Immediately after induction, neuromuscular function was continuously monitored by acceleration of thumb adduction using an acceleration transducer (nerve stimulator: Myograph 2000, Biometer, Odense, Denmark) in response to supramaximal singletwitch (0.2 ms duration, 0.1 Hz) stimulation of the ulnar nerve at the wrist. When the twitch tension became stable and was determined as the control, the magnesium group received an intubating dose of vecuronium 0.085 mg·kg^{-1} and magnesium sulfate 40 mg·kg^{-1}, while the control group received an equivalent volume of vecuronium and saline as a bolus. All patients received an intubating dose of vecuronium at 4–5 min after the priming dose. Onset time (time from the injection of the intubating dose to 80% depression of twitch tension) and duration of action (time from 80% depression to the recovery of twitch tension to 20% of control) of vecuronium were determined. At 80% depression, direct laryngoscpy was performed. The intubation conditions were not evaluated. After tracheal intubation, anesthesia was maintained with 66% nitrous oxide, 34% oxygen, and 2.0% or less sevoflurane.

ECG was monitored continuously and blood pressure was measured noninvasively using an automatic oscillometric device every 1 min. Heart rate and mean arterial blood pressure before injection of the priming dose were determined as the baselines. The peak values for the first 3 min after intubation were determined. Blood samples were obtained before injection of the priming dose, at 2 min after intubation, and at 30, 60, and 90 min after injection of the intubating dose. Serum magnesium was measured by the colorimetric method using xylidilblue as a chromophore. Fractionated plasma catecholamine concentrations were measured by high-performance liquid chromatography.

The unpaired Student's t test was used for statistical analysis. Significance was defined as $P < 0.01$. Results are presented as mean ± SD.

Results

There was no significant difference in patient characteristics between the two groups (Table 1). Heart rate and mean arterial blood pressure after intubation increased above the baseline in all patients. The percent change from baseline in mean arterial pressure after intubation was significantly smaller in the magnesium group than in the control group, but the percent change in heart rate was similar (Table 2). There were no significant changes in plasma catecholamine concentrations after intubation in either group (Table 2).

Vecuronium onset time was significantly shorter in the magnesium group than in the control group (Table 3). Duration of vecuronium was significantly longer in

Table 1. Patient characteristics

Group	No. of patients	Gender		Age (years)	Height (cm)	Weight (kg)
		M	F			
Control	20	10	10	49 ± 18	160 ± 7	59 ± 10
Magnesium	20	10	10	48 ± 16	164 ± 8	61 ± 8

Table 2. Changes from baseline in hemodynamic variables and plasma catecholamine concentrations induced by tracheal intubation

Group	MAP before intubation (mmHg)	MAP after intubation (mmHg)	Percent change in MAP (%)	HR before intubation (·min^{-1})	HR after intubation (·min^{-1})	Percent change in HR (%)	Epinephrine (ng·ml^{-1})		Norepinephrine (ng·ml^{-1})	
							Baseline	After intubation	Baseline	After intubation
Control	88 ± 12	112 ± 18	24 ± 13	76 ± 15	96 ± 17	25 ± 16	6.3 ± 3.4	4.0 ± 2.1	27.0 ± 10.1	33.4 ± 16.1
Magnesium	92 ± 11	104 ± 14	13 ± 10*	77 ± 14	94 ± 12	27 ± 25	4.8 ± 2.9	4.5 ± 2.8	26.4 ± 10.6	37.2 ± 14.2

MAP, mean arterial pressure; HR, heart rate.
* $P < 0.01$, compared with control group.

the magnesium group than the control group (Table 3). Serum magnesium concentration increased to 4.36 ± 0.42 mg·dl^{-1} (1.80 ± 0.73 mmol·l^{-1}) 2 min after intubation, and at 90 min after its administration, it was still significantly higher than the baseline value (Table 4).

Discussion

In the present study, vecuronium onset time was significantly reduced in the magnesium group compared to the control group. James et al. [7] investigated the effect of magnesium on the pancuronium onset time and concluded that pretreatment with magnesium does not significantly accelerate the onset of action of magnesium. However, they compared magnesium pretreatment not to nonmagnesium pretreatment, but to the priming principle, with the result that there was no significant difference in pancuronium onset time between the two techniques. Their result shows that magnesium pretreatment has an effect equivalent to pancuronium priming on the onset time of pancuronium apart from the question of usefulness. In our result, vecuronium onset time in the magnesium group was shortened by the additive effects produced by both vecuronium priming and magnesium pretreatment. Shortening the onset time of vecuronium and prolonging its duration of action by administering magnesium may be advantageous during relatively prolonged surgical procedures. However, this technique should be used with caution in briefer surgical procedures to obtain adequate recovery of muscular strength at the end of the procedures [10,11].

Because the purpose of the present study was not to refine the priming principle, but to evaluate the ability of magnesium in tracheal intubation using the vecuronium priming principle, we arbitrarily set the total dose, the priming dose, and the intubating dose at 0.1 mg·kg^{-1}, 0.015 mg·kg^{-1} (15% of the total dose), and 0.085 mg·kg^{-1} (the total dose minus the priming dose), respectively, considering that these doses have been reported to be effective and safe in the literature [12–16].

The priming dose of 0.015 mg·kg^{-1} was reported to cause certain symptoms of partial neuromuscular blockade such as blurred vision and ptosis but no breathing difficulties [13,14]. Taboada et al. [14] and Heumer et al. [16] reported that the optimal priming interval is 4 min, and Heumer et al. [16] found no difference between 4 and 5 min using the priming dose of 0.015 mg·kg^{-1}. In agreement with these reports, anesthesia was induced 3 min after the priming dose, with the result that the patients received the intubating dose at 4–5 min after the priming dose.

The normal serum magnesium level is 1.9–2.5 mg·dl^{-1} (0.79–1.03 mmol·l^{-1}). The therapeutic range of serum magnesium concentrations for the treatment of preeclamptic toxemia has been observed to be 8.4–9.7 mg·dl^{-1} empirically [5,17]. James et al. [18] investigated the effect of magnesium on the onset of muscle relaxation, the intensity of blockade, the duration of paralysis, and the increase in potassium produced by succinylcholine at the time of intubation. They concluded that magnesium had no significant effect on the characteristics of the paralysis, but prevented the increase in potassium. James et al. [19] also investigated the ability of magnesium to inhibit cardiovascular response and catecholamine release at the time of intubation with succinylcholine, concluding that magnesium sulfate attenuated the catecholamine-mediated cardiovascular response after tracheal intubation. In these studies they followed empirical obstetric guidelines by raising serum magnesium concentrations to 4.8–9.7 mg·dl^{-1} using a single bolus of 60 mg·kg^{-1} magnesium sulfate. The mean serum magnesium concentrations after intubation were 7.0 ± 1.67 mg·dl^{-1} and 7.1 ± 1.36 mg·dl^{-1} in these reports. James et al. [7] also used 60 mg·kg^{-1} magnesium sulfate pretreatment to compare its effect on pancuronium onset time with the priming principle. The mean serum magnesium concentration at the time of intubation in the magnesium pretreatment group was 5.6 ± 1.52 mg·dl^{-1}. This is the only report with regard to the effect of magnesium on the onset time of nondepolarizing muscle relaxants. In the present study we set the single bolus of magnesium at 40 mg·kg^{-1}, not for empirical obstetric reasons, but on the basis of recent reports [20–26] regarding the cardiovascular effects of magnesium. Iseri et al. [25]

Table 3. Onset time and duration of action of vecuronium

Group	Onset time (s)	Duration of action (min)
Control	113 ± 37	39 ± 11
Magnesium	76 ± 32*	58 ± 15*

*$P < 0.01$, compared with control group.

Table 4. Serum magnesium concentrations in the magnesium group

Serum magnesium	Before priming (baseline)	2 min after intubation	30 min	60 min	90 min
mg·dl^{-1}	2.04 ± 0.17	4.36 ± 0.42*	3.05 ± 0.10*	2.78 ± 0.13*	2.67 ± 0.19*

*$P < 0.01$ versus baseline.
1 mg·dl^{-1} = 0.41 mmol·l^{-1}.

reported that mean serum magnesium concentrations of 4.4 mEq·l^{-1} (5.3 mg·dl^{-1}) and 3.27 mEq·dl^{-1} (3.96 mg·dl^{-1}) were efficacious against ventricular and supraventricular tachyarrhythmia, respectively. More recently, Iseri [26] reported that a serum magnesium concentration of 4 mEq·l^{-1} (4.84 mg·dl^{-1}) controlled intractable ventricular tachycardia (VT) and ventricular fibrillation (VF) in 12 patients, and that the maximal average concentration of 3.49 mEq·l^{-1} (4.22 mg·dl^{-1}) converted multifocal atrial tachycardia in 7 of the 8 patients to sinus rhythm. In the present study the mean serum magnesium concentration after intubation reached 3.60 ± 0.35 mEq·l^{-1} (4.36 ± 0.42 mg·dl^{-1}), which was within this antiarrhythmic therapeutic range.

Cardiovascular response and catecholamine release associated with tracheal intubation in the present study were different from those in the report of James et al. [19]. They reported that the increases in heart rate, systolic blood pressure, and catecholamine release in the magnesium group were significantly smaller than those in the control group. In the present study, the percent change in mean arterial pressure in the magnesium group was significantly smaller than that in the control group, but there was no significant difference between the two groups with regard to percent changes in heart rate and plasma catecholamine concentration after intubation; the latter did not differ significantly from baseline in either group. Therefore, the significant difference between the two groups with respect to percent change in mean arterial pressure is not due to the adrenergic antagonist action of magnesium but rather to its vasodilator action. The effects of magnesium on heart rate are a little complicated [5,19,27]. Magnesium directly affects the sinoatrial (SA) node in isolated animal hearts to slow the atrial rate by inhibiting the calcium-mediated depolarizing current in pacemaker tissue. However, the reduction in arterial blood pressure produced by magnesium reduces vagal tone, and magnesium inhibits the release of acetylcholine from the vagus nerve to increase heart rate. In the present study these two effects may have offset each other. Therefore, disregarding catecholamine release, the percent change in heart rate did not differ between the two groups.

In conclusion, the present study demonstrates that vecuronium priming with magnesium inhibits the increase in mean arterial pressure and significantly shortens the onset time of vecuronium but prolongs its duration of action, and therefore should be used in careful consideration of its indication.

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