

Interaction of magnesium sulphate with vecuronium-induced neuromuscular block†

T. FUCHS-BUDER, O. H. G. WILDER-SMITH, A. BORGEAT AND E. TASSONYI

Summary

We have investigated the interaction between magnesium sulphate 40 mg kg⁻¹ i.v. and vecuronium. First, we determined the effect of pretreatment with magnesium on the potency of vecuronium using a single bolus dose–response technique. In addition, we compared the time course of vecuronium-induced neuromuscular block (vecuronium 100 µg kg⁻¹) with and without magnesium pretreatment. For both parts, neuromuscular block was assessed by electromyography. In addition, the effect of magnesium pretreatment on vecuronium-induced neuromuscular block was investigated in the context of rapid sequence induction of anaesthesia. We found that the neuromuscular potency of vecuronium was increased by pretreatment with magnesium sulphate. The ED₅₀ and ED₉₀ of vecuronium with MgSO₄ were 25% lower than without MgSO₄ (ED₅₀: 21.3 vs 26.9 µg kg⁻¹; ED₉₀: 34.2 vs 45.7 µg kg⁻¹; *P* < 0.05 for both). Mean onset time was 147.3 (SD 22.2) s in the MgSO₄–vecuronium group vs 297.3 (122) s for controls (*P* < 0.05). Clinical duration was prolonged (MgSO₄–vecuronium 43.3 (9) min vs 25.2 (5.1) min for controls; *P* < 0.05). This was also true for the recovery index (20.1 (6.6) min vs 10.6 (3.4) min; *P* < 0.05) and duration to 75% recovery (63.4 (9.9) min vs 35.8 (6.9) min; *P* < 0.05). In the context of rapid sequence induction, pretreatment with MgSO₄ improved the intubating score of vecuronium compared with vecuronium without MgSO₄, reaching the same quality as that with suxamethonium 1 mg kg⁻¹. We conclude that magnesium pretreatment increased the neuromuscular potency of vecuronium, in addition to modifying the time course of its neuromuscular block. (*Br. J. Anaesth.* 1995; 74: 405–409)

Key words

Neuromuscular block, vecuronium. Ions, magnesium sulphate. Measurement techniques, electromyography. Pharmacology, dose–response.

Magnesium sulphate (MgSO₄) has long been used in the treatment of pre-eclampsia and hypertension [1,2]. In addition, MgSO₄ is increasingly used for haemodynamic control during anaesthesia [3, 4]. In a recent study it has been demonstrated that MgSO₄ as an adjuvant to general anaesthesia may modulate

nociception, probably via its interaction with the NMDA receptor-associated calcium ionophore [5, 6]. Thus there are several situations in which the anaesthetist may be faced with a patient treated with MgSO₄ undergoing general anaesthesia. It is well known that MgSO₄ inhibits acetylcholine release at motor nerve terminals [7]; consequently it may enhance the effect of neuromuscular blockers. Ghoneim and Long [1] found that MgSO₄ potentiated the neuromuscular block of depolarizing and non-depolarizing neuromuscular blockers, as was reported by Giesecke and colleagues [8]. Sinatra and colleagues [9] reported on a pre-eclamptic patient in whom the duration of vecuronium-induced neuromuscular block was prolonged markedly after pretreatment with MgSO₄. Similar results have been reported by Skaredoff, Roaf and Datta [10]. However the interaction of MgSO₄ and vecuronium bromide has not been systematically investigated so far.

The aims of the present study were to establish a dose–response relationship for vecuronium in patients with and without MgSO₄ pretreatment, and to study the time course of vecuronium-induced neuromuscular block with and without MgSO₄. In addition, we wished to see if pretreatment with MgSO₄ improved intubating conditions in a clinically relevant way when using vecuronium for rapid sequence induction.

Patients and methods

After obtaining institutional Ethics Committee approval and written informed consent, we studied 125 patients, ASA I or II, undergoing elective surgery. Patients were excluded if they were known to have neuromuscular disease or were receiving medications known to influence neuromuscular function. All patients were premedicated with midazolam 7.5 mg orally 1 h before arrival in the operating room.

In the first part of the study, 60 patients were allocated randomly to two groups of 30 patients each (groups A and B) for the study of dose–response

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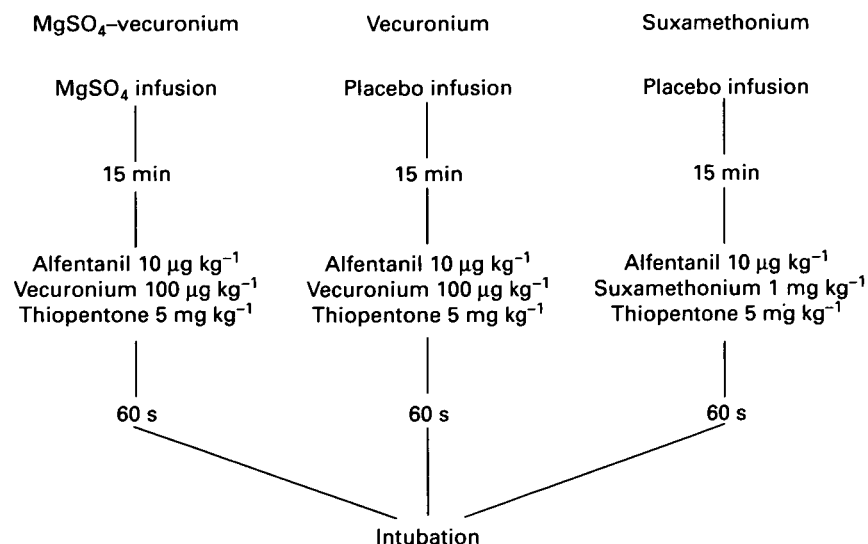


Figure 1 Flow diagram of rapid sequence induction study design.

relationships using a single bolus technique. Fifteen minutes before induction of general anaesthesia, patients in group A received MgSO_4 40 mg kg^{-1} in saline as an i.v. infusion over 15 min. Patients in group B received the same volume of saline without MgSO_4 . In both groups anaesthesia was induced with fentanyl 2 µg kg^{-1} and thiopentone 5 mg kg^{-1} and maintained with 60% nitrous oxide in oxygen via a face mask until tracheal intubation. During the study end-tidal carbon dioxide concentration was maintained at 4.5–5 vol% (Normocap, Datex Instrumentarium Corporation, Finland). Neuromuscular transmission was assessed by electromyography (Relaxograph, Datex Instrumentarium Corporation, Helsinki) at the left ulnar nerve–hypotenar muscle using transcutaneous electrodes. Measurements commenced when anaesthesia had been induced. The Relaxograph was set to deliver supramaximal stimuli (0.1 ms duration) of train-of-four (TOF) at 2 Hz every 20 s. The first of the four evoked responses was considered the twitch height. To minimize movement-induced changes in twitch response during electromyography, the patient's hand was fixed carefully to avoid electrode displacement.

After stabilization of the EMG recording, one of the following doses of vecuronium was administered: 15, 25 or 35 µg kg^{-1} in group A ($n = 10$ for each dose) and 15, 30 or 45 µg kg^{-1} in group B ($n = 10$ for each dose). Maximum depression of the twitch response was measured and recorded, with each patient acting as their own control.

In the second part of the study, another 20 patients were allocated randomly to group C ($n = 10$) or D ($n = 10$) to study the influence of pretreatment with MgSO_4 on the time constants of vecuronium-induced neuromuscular block. Patients in group C received MgSO_4 in a manner identical to the first part of the study, while patients in group D received saline alone. Anaesthesia was induced with fentanyl 2 µg kg^{-1} and thiopentone 5 mg kg^{-1} , and maintained with 1% isoflurane, and 60% nitrous oxide in oxygen via a face mask. When the end-tidal isoflurane concentration had stabilized, the Relaxo-

graph was recalibrated and the control twitch height determined. Patients in both groups then received vecuronium 100 µg kg^{-1} as an i.v. bolus and the following intervals were measured: onset time = time between administration of vecuronium and maximum twitch depression; clinical duration (CD) = time between administration of vecuronium and recovery to 25% twitch height; recovery index (RI) = time from 25% to 75% twitch height recovery; and duration 75 = time between administration of vecuronium and recovery to 75% twitch height.

End-tidal carbon dioxide concentration, body temperature and isoflurane concentrations were maintained stable during the whole study (4.5–5 vol%, 36.0–36.5 °C, 0.8–1%, respectively). Patients did not receive further neuromuscular blockers until recovery to $100\% \pm 5\%$ twitch height. Patients in whom twitch height did not recover to control levels were excluded from the study. For group C and D patients, we also determined the plasma concentrations of magnesium before and 15 min after the end of the MgSO_4 or placebo infusion.

In the third part of the study we assessed the quality of neuromuscular block in the context of rapid sequence induction. Anaesthesia was induced with alfentanil 10 µg kg^{-1} , thiopentone 5 mg kg^{-1} and different types of neuromuscular block (fig. 1). Forty-five patients were allocated randomly to one of three neuromuscular block techniques ($n = 15$ per group). The first group was pretreated with MgSO_4 40 mg kg^{-1} in 100 ml of saline 15 min before rapid sequence induction and neuromuscular block with vecuronium 100 µg kg^{-1} . The second group received 100 ml of saline as placebo pretreatment, again 15 min before rapid sequence induction and neuromuscular block with vecuronium 100 µg kg^{-1} . The third group received suxamethonium 1 mg kg^{-1} for neuromuscular block 15 min after 100 ml of saline placebo. Sixty seconds after induction the trachea was intubated in all patients by the same experienced anaesthetist blinded to the treatment (fig. 1). He assessed the intubating conditions in each patient using the following criteria [11]: excellent = jaw relaxed, vocal cords abducted and immobile, and no

Table 1 Patient data (mean (SD or range))

	Dose-response		Time course		Intubating conditions		
	MgSO ₄ -vecuronium	Vecuronium	MgSO ₄ -vecuronium	Vecuronium	MgSO ₄ -vecuronium	Vecuronium	Suxamethonium
M/F	20/10	17/13	6/4	5/5	8/7	9/6	8/7
Age (yr)	42 (19-55)	42 (19-61)	36 (18-53)	35 (24-55)	43 (21-64)	42 (21-65)	42 (19-63)
Weight (kg)	69 (9)	71 (12)	67 (9)	65 (17)	69 (12)	69 (11)	66 (13)

diaphragmatic movement; good = jaw relaxed, vocal cords abducted and immobile, but some diaphragmatic movement; poor = jaw relaxed, vocal cords moving, and coughing; and inadequate = jaw not relaxed and vocal cords closed.

Vecuronium dose-effect relationships for groups A and B were determined using linear regression analysis after log transformation of the doses and logit transformation of the twitch responses (log dose *vs* logit effect). To compare the neuromuscular potency of vecuronium with or without pretreatment with MgSO₄ the values of ED₅₀ and ED₉₀ were calculated for each group from the regression slopes. The regression slopes were tested for parallelism by analysis of covariance. The ED₅₀ and ED₉₀ values between the two groups were compared using an unpaired *t* test. For statistical comparison of the time constants of vecuronium-induced neuromuscular block in patients pretreated or not pretreated with MgSO₄, the Mann-Whitney *U* test was used. Intubating conditions were analysed using the Kruskal-Wallis test after assigning a numeric value to each intubation score.

All values apart from intubating condition scores are expressed as mean (SD) or 95% confidence limits. For statistical comparisons, differences were considered significant when *P* < 0.05.

Results

The study groups did not differ in age, sex distribution or weight (table 1).

DOSE-RESPONSE STUDY

The regression lines of the dose-response curves did not deviate significantly from parallelism (fig. 2). Values for the slope, *Y*-intercept, coefficient of correlation (*r*), ED₅₀ and ED₉₀ are shown in table 2. ED₅₀ of vecuronium was 21.3 µg kg⁻¹ in the MgSO₄ pretreated group compared with 26.9 µg kg⁻¹ without MgSO₄ (*P* < 0.05); ED₉₀ was 34.2 µg kg⁻¹ in the MgSO₄ pretreated group compared with 45.7 µg kg⁻¹ in controls (*P* < 0.05).

TIME COURSE OF NEUROMUSCULAR BLOCK

The onset time was 147.3 (22.2) s in the MgSO₄ group compared with 297.3 (122) s in controls (*P* < 0.05). The clinical duration was longer in the MgSO₄ group (43.3 (9) min) compared with controls (25.2 (5.1) min; *P* < 0.05). The same was true for the recovery index (20.1 (6.6) min *vs* 10.6 (3.4) min, respectively; *P* < 0.05) and for recovery to 75% of

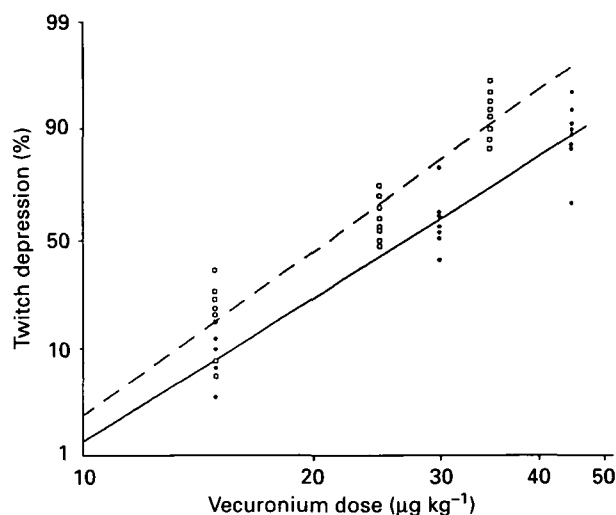


Figure 2 Single bolus dose-response curves (log dose *vs* logit effect) for vecuronium with (---) and without (—) MgSO₄. Some individual data points are superimposed.

Table 2 Neuromuscular potency of vecuronium with and without MgSO₄ (mean (95% confidence limits)). **P* < 0.05

	MgSO ₄ -vecuronium	Vecuronium
<i>n</i>	30	30
<i>r</i>	0.954	0.967
ED ₅₀ (µg kg ⁻¹)	21.3* (20.7-22.3)	26.9 (25.8-28.3)
ED ₉₀ (µg kg ⁻¹)	34.2* (32.1-36.5)	45.7 (43.3-49.9)
Slope	4.6	4.1
<i>Y</i> -intercept	-6.2	-5.9

Table 3 Time course of neuromuscular block (mean (SD)). CD = Clinical duration, RI = recovery index; D75 = duration until 75% recovery of twitch height. **P* < 0.05

	MgSO ₄ -vecuronium	Vecuronium
Onset (s)	147.3 (22.2)*	297.2 (122)
CD (min)	43.3 (9)*	25.2 (5.1)
RI (min)	20.1 (6.6)*	10.6 (3.4)
D75 (min)	63.4 (9.9)*	35.8 (6.9)

the twitch height (63.4 (9.9) min in the MgSO₄ group *vs* 35.8 (6.9) min in controls; *P* < 0.05) (table 3).

Plasma magnesium concentrations are shown in table 4; they increased from a baseline concentration of 0.9 (0.06) to 1.08 (0.07) mmol litre⁻¹ 15 min after the MgSO₄ infusion (*P* < 0.05); in controls plasma magnesium concentrations were 0.86 (0.08) mmol litre⁻¹ before and 0.87 (0.6) mmol

Table 4 Plasma magnesium concentrations (mmol litre⁻¹) (mean (SD)). T1 = Baseline concentrations before infusion; T2 = values 15 min after the end of infusion. **P* < 0.05 compared with baseline levels; †*P* < 0.05 compared with magnesium group at T2.

	MgSO ₄ (40 mg kg ⁻¹)	Placebo (0.9% NaCl)
T1	0.9 (0.06)	0.86 (0.08)
T2	1.08 (0.07)*	0.87 (0.06)†

Table 5 Intubating conditions. Criteria for intubating conditions; excellent = jaw relaxed, vocal cords abducted and immobile, no diaphragmatic movement; good = jaw relaxed, vocal cords abducted and immobile, some diaphragmatic movement; poor = jaw relaxed, vocal cords moving, coughing; inadequate = jaw not relaxed, vocal cords closed. **P* < 0.05 compared with MgSO₄-vecuronium and suxamethonium groups.

	MgSO ₄ -vecuronium	Vecuronium*	Suxamethonium
Excellent	10	1	14
Good	5	5	1
Poor	0	9	0
Inadequate	0	0	0

litre⁻¹ after the infusion (ns), respectively. The plasma magnesium concentrations after the MgSO₄ infusion were higher than after the placebo infusion (*P* < 0.05). The magnesium infusions were well tolerated, with no signs of muscular weakness. The only discomfort described by patients was a hot flush of the lower abdomen reported by 21 of the 55 patients.

INTUBATING CONDITIONS

Intubating conditions after pretreatment with MgSO₄ were significantly better than those obtained with vecuronium alone, and did not differ from those obtained with suxamethonium (table 5).

Discussion

We have shown that the neuromuscular potency of vecuronium was increased markedly by MgSO₄, the respective ED₅₀ and ED₉₀ values were 20–25% lower in the magnesium group. For vecuronium without MgSO₄, we found an ED₅₀ of 26.9 µg kg⁻¹ and an ED₉₀ of 45.7 µg kg⁻¹. These data are in accordance with the results of other studies in which the single bolus technique has been used [12, 13].

In order to quantify this interaction we used the single bolus dose–response technique instead of the cumulative technique described for long-acting neuromuscular blockers [14]. The latter technique may not be appropriate for vecuronium, as larger potency estimates are obtained by this method than with the single bolus technique [15]. This may arise because the effect of the initial dose of vecuronium has terminated before the last dose is given. For constructing the dose–response curves we used lower doses of vecuronium in patients pretreated with MgSO₄. This was necessary because in the pilot dose–finding study we found that doses of vecuronium as high as 45 µg kg⁻¹ resulted in 100% block of

neuromuscular transmission after pretreatment with MgSO₄. This would not have permitted correct construction of a dose–response relationship.

We administered relatively low doses of MgSO₄ (i.e. 40 mg kg⁻¹). We chose this dose as it is currently used in our institution for obstetric patients. Even such small doses of MgSO₄ markedly increased the neuromuscular potency of vecuronium. This may be explained on the basis that the plasma concentration of magnesium was higher 15 min after MgSO₄ infusion than before, and higher than in controls. Non-depolarizing neuromuscular blockers have both presynaptic and postsynaptic activity at the neuromuscular junction [16]. Presynaptic action is thought to occur at nicotinic receptors on the nerve terminals that mediate autofacilitation of acetylcholine release, while the postsynaptic action inhibits end-plate depolarization [17]. MgSO₄ has mainly presynaptic effects by inhibiting acetylcholine release at motor nerve terminals [7], effects which may be responsible for the interaction with vecuronium.

In the second part of the study we examined the influence of MgSO₄ on the time course of the neuromuscular block. We used the so-called “intubating dose” of vecuronium (i.e. 100 µg kg⁻¹). With this dose we found a clinical duration of action of about 25 min. However, after pretreatment with MgSO₄ the duration of vecuronium block was nearly doubled. The rapid recovery of neuromuscular function after vecuronium contributes to its safety in clinical practice. MgSO₄ decreases the recovery rate of vecuronium and considerably prolongs the time to achieve safe extubation conditions. A longer clinical duration of action together with slower recovery after an intubating dose of vecuronium when used together with magnesium results in a change in the total duration of vecuronium-induced curarization. In this context vecuronium no longer has the profile of an intermediate-acting neuromuscular blocker.

The speed of onset of neuromuscular block for vecuronium was increased markedly in the MgSO₄ group; about 2 min compared with 5 min in the controls. This is in accordance with the study of Lampl and Dandoy [18], where the speed of onset of atracurium was increased markedly when patients were pretreated with MgSO₄. James, Schenk and Van Der Veen reported similar results for pancuronium [19]; an onset time of 68.3 s after MgSO₄ pretreatment. The shorter onset time of vecuronium after MgSO₄ pretreatment may be a clinically interesting phenomenon, because it may contribute to improvement in intubating conditions.

To test this hypothesis, we determined the intubating scores for rapid sequence induction with vecuronium 100 µg kg⁻¹ with and without MgSO₄ pretreatment and compared them with those obtained after suxamethonium, the gold standard for rapid sequence induction. The intubating scores for the group receiving vecuronium and MgSO₄ pretreatment at 60 s after the rapid sequence induction were better than in those receiving vecuronium alone, and similar to the scores obtained after suxamethonium. When using vecuronium 100 µg kg⁻¹ without MgSO₄, intubation after 60 s was not ideal, but always possible. This may be

explained by the findings of Donati, Meistelman and Plaud [20] that the onset of neuromuscular block after vecuronium is faster for the larynx than for peripheral muscles.

The increase in plasma concentration of magnesium in patients pretreated with $MgSO_4$ was statistically significant, but clinically safe as no symptoms of muscle weakness were reported by the patients. This is in accordance with the results of Baraka and Yazigi [21] who found no clinical or electromyographic signs of muscle weakness even at slightly higher plasma magnesium concentrations ($1.7\text{--}2.5\text{ mmol litre}^{-1}$). These data indicate that pretreatment with $MgSO_4$ 40 mg kg^{-1} does not induce any degree of measurable neuromuscular block when administered before the non-depolarizing blocker. Thus pretreatment with $MgSO_4$ 40 mg kg^{-1} is safe. $MgSO_4$ before vecuronium improves the intubating conditions of vecuronium for rapid sequence induction, and thus may be a useful clinical alternative for rapid sequence induction in some patients in whom the use of suxamethonium is contraindicated or controversial.

We conclude that $MgSO_4$, administered before vecuronium, accelerated the onset of neuromuscular block necessary for intubation of the trachea, that $MgSO_4$ in the presence of vecuronium intensified and prolonged neuromuscular block, and that monitoring of neuromuscular function and reduction in dose of vecuronium are required when using these two drugs in combination.

References

- Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; **32**: 23–27.
- James MFM. Clinical use of magnesium infusions in anesthesia. *Anesthesia and Analgesia* 1992; **74**: 129–136.
- Zaloga G, Eisenach JC. Magnesium, anesthesia, and hemodynamic control. *Anesthesiology* 1991; **74**: 1–2.
- England MR, Gorden G, Salem M, Chernow B. Magnesium administration and dysrhythmias after cardiac surgery. *Journal of the American Medical Association* 1992; **268**: 2395–2402.
- Wilder-Smith OHG, Hoffmann AC, Borgeat A, Rifat K. Fentanyl or magnesium analgesic supplementation. Effect on postoperative sensory thresholds. *Anesthesiology* 1992; **77**: A208.
- Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature (London)* 1984; **307**: 462–465.
- Krendal DA. Hypermagnesemia and neuromuscular transmission. *Seminars in Neurology* 1990; **10**: 42–45.
- Giesecke AH, Morris RE, Dalton MD, Stephen CR. Of magnesium, muscle relaxants, toxic paralytics, and cats. *Anesthesia and Analgesia* 1968; **47**: 689–695.
- Sinatra RS, Philip BK, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulphate. *Anesthesia and Analgesia* 1985; **64**: 1220–1222.
- Skaredoff MN, Roaf ER, Datta S. Hypermagnesaemia and anaesthetic management. *Canadian Anaesthetists Society Journal* 1982; **29**: 35–41.
- Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology* 1993; **79**: 913–918.
- Ørding H, Skovgaard LT, Engbæk J, Viby Mogensen J. Dose-response curves for vecuronium during halothane and neuroleptanaesthesia: Single bolus versus cumulative method. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 121–124.
- O'Hara DA, Fragen RJ, Shanks CA. The effect of age on the dose-response curves for vecuronium in adults. *Anesthesiology* 1985; **63**: 542–544.
- Donlon JV, Savarese JJ, Ali HH, Teplik RS. Human dose-response curves for neuromuscular blocking drugs. *Anesthesiology* 1980; **53**: 161–166.
- Fisher DM, Fahey MR, Cronnelly R, Miller RD. Potency determination of vecuronium (ORG NC45). *Anesthesiology* 1982; **57**: 309–310.
- Camkin NTA, Hood JR, Feldman SA. Resistance to decamethonium neuromuscular block after prior administration of vecuronium. *Anesthesia and Analgesia* 1993; **77**: 78–80.
- Bowman WC. Prejunctional and postjunctional cholinergic receptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; **59**: 935–943.
- Lampl E, Dandoy M. Priming of atracurium with magnesium. *British Journal of Anaesthesia* 1993; **70**: A139.
- James MFM, Schenk PA, Van Der Veen BW. Priming of pancuronium with magnesium. *British Journal of Anaesthesia* 1991; **66**: 247–249.
- Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. *Anesthesiology* 1991; **74**: 833–837.
- Baraka A, Yazigi A. Neuromuscular interaction of magnesium with succinylcholine-vecuronium sequence in the eclamptic parturient. *Anesthesiology* 1987; **67**: 806–808.