Antagonism of vecuronium-induced neuromuscular block in patients pretreated with magnesium sulphate: dose–effect relationship of neostigmine†

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†Presented in part at the ESA Annual Meeting, Barcelona, Spain, April 1998

We have investigated the dose–effect relationship of neostigmine in antagonizing vecuronium-induced neuromuscular block with and without magnesium sulphate (MgSO4) pretreatment. Neuromuscular block was assessed by electromyography with train-of-four (TOF) stimulation. First, we determined neostigmine-induced recovery in patients pretreated with MgSO4 (group A) or saline (group B) (n=12 each). The height of T1, 5 min after neostigmine, was 43 (7)% in group A and 65 (6)% in group B (P<0.01). Respective values after 10 min were 59 (7)% and 83 (5)% (P<0.01). TOF ratio, 5 min after neostigmine, was 29 (6)% in group A and 29 (5)% in group B. Respective values after 10 min were 38 (11)% and 51 (7)% (P<0.01). To gain insight into the mechanisms leading to delayed recovery after MgSO4, we calculated assisted recovery, defined as neostigmine-induced recovery minus mean spontaneous recovery. Spontaneous recovery was assessed in another 24 patients. Patients in group C received MgSO4/vecuronium and patients in group D vecuronium only (n=12 each). Five minutes after neostigmine, assisted recovery was 22 (7)% in the MgSO4 pretreated patients and 28 (6)% in controls (P<0.05). Ten minutes after neostigmine, values were 24 (7)% and 22 (6)%. Maximum assisted recovery was not influenced by MgSO4 pretreatment (27 (6)% in group A and 32 (6)% in group B) and time to maximum effect was comparable between groups: 6 (4–10) min and 7 (5–8) min, respectively. We conclude that neostigmine-induced recovery was attenuated in patients treated with MgSO4. This was mainly a result of slower spontaneous recovery and not decreased response to neostigmine.

Br J Anaesth 1999; 82: 61–5

Keywords: antagonists neuromuscular block, neostigmine; neuromuscular block, vecuronium; pharmacology, magnesium sulphate; monitoring, electromyography

Accepted for publication: August 12, 1998

Magnesium sulphate (MgSO4) is used during anaesthesia for its antihypertensive and anti-arrhythmic properties, and as an anticonvulsant for women with eclampsia.1–3 There has been a substantial increase in the use of MgSO4 as an anticonvulsant in pregnancy. In 1992, only 2% of obstetricians in the UK used MgSO4 for this indication; 4 yr later, 40% reportedly used it in pre-eclampsia and 60% in eclampsia.4 Anaesthetists may therefore have to manage a patient treated with MgSO4.

At the motor nerve terminal, MgSO4 inhibits acetylcholine release; thus it enhances the effect of neuromuscular blocking agents. It has been demonstrated that pretreatment with MgSO4 increases the clinical duration and recovery index of neuromuscular blocking agents.5–12 This may have clinical consequences, leading to incomplete neuromuscular recovery and residual paralysis at the end of surgery.13–15 Thus quantitative data on the effect of anticholinesterase drugs in patients receiving MgSO4 are needed for safe management of neuromuscular block. However, data from prospective, controlled studies investigating this issue are lacking. In this study, we have investigated the dose–effect relationship of neostigmine in antagonizing vecuronium-induced neuromuscular block with and without MgSO4 pretreatment. In addition, the incidence of side effects after anticholinesterase treatment, such as bradycardia, tachycardia or arrhythmia, was assessed in both groups.

Patients and methods
After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 48 patients,
ASA I or II, undergoing elective surgery of at least 120 min duration, in a double-blinded manner. Patients with neuromuscular disease or receiving medications known to interact with neuromuscular function were excluded, as were those with electrolyte abnormalities. All patients were premedicated with midazolam 7.5 mg orally, 1 h before arrival in the operating room.

Patients were allocated randomly to one of four groups (n=12 each). In groups A and B, neostigmine-induced antagonism of vecuronium with and without MgSO4 pretreatment was studied. In groups C and D, we assessed spontaneous recovery from vecuronium-induced neuromuscular block with and without MgSO4 pretreatment. Fifteen minutes before induction of anaesthesia, patients in groups A and C received MgSO4 60 mg kg⁻¹ in saline as an i.v. infusion over 15 min. Patients in groups B and D received the same volume of saline without MgSO4. Anaesthesia was induced in all groups with fentanyl and antagonist of vecuronium with and without MgSO4 pretreatment. Patients with electrolyte abnormalities. All patients were premedicated with midazolam 7.5 mg orally, 1 h before arrival in the operating room.

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The degree of assisted recovery of T1, defined as actual recovery after anticholinesterase minus mean spontaneous recovery, was calculated. This was done by subtracting mean spontaneous recovery obtained in group C from individual recovery values in group A, and by subtracting mean spontaneous recovery in group D from individual recovery values in group B. Thus assisted recovery was assessed once every minute for a fixed time interval (10 min) after injection of the reversal agent. In addition, maximum assisted recovery and time to maximum effect were assessed in both groups.

To study the influence of MgSO4 pretreatment on the cardiovascular effect of neostigmine-induced reversal, the incidence of bradycardia, tachycardia and arrhythmia was assessed in the four groups. Bradycardia was defined as a decrease in heart rate of at least 20% and tachycardia as an increase of at least 20%. Heart rate immediately before neostigmine was taken as baseline.

For statistical analysis, group A was compared with group B, and group C was compared with group D. Physical characteristics were analysed using the Mann–Whitney U test. For statistical comparison of neostigmine-induced recovery, spontaneous recovery and assisted recovery, the Mann–Whitney U test was used. All values are expressed as mean (SD) or median (range) (time to maximum assisted recovery, age). For statistical comparisons, differences were considered significant when P<0.05. Estimation of sample size was based on the results of the study of Smith, Donati and Bevan. Statistical analysis was performed using the StatView software package (StatView for Macintosh, release 4.5.1, 1995 Abacus Concepts, Berkeley, CA, USA).

Results

The groups did not differ in age, sex distribution or weight (Table 1). The time course of vecuronium-induced neuromuscular block is given in Table 2.

**Neostigmine-induced recovery**

Recovery of T1 during the 10-min period after administration of neostigmine 0.02 mg kg⁻¹ and atropine 0.01 mg kg⁻¹ was less in patients pretreated with MgSO4 compared with controls; respective values after 5 min were 43 (8)% and 66 (6)% (P<0.01) and after 10 min, 60 (8)% and 83 (6)% respectively (P<0.01) (Fig. 1, Table 3). TOF ratio 5 min after neostigmine was 29 (6)% in group A and 29 (5)% in group B. The respective values after 10 min were 38 (11)% and 51 (7)% (P<0.01).

**Spontaneous recovery**

During the 10-min period after T1 reached 10%, spontaneous recovery was significantly slower in patients pretreated with MgSO4 compared with controls (5 min, 21 (3)% vs 38 (8)% (P<0.01); 10 min, 35 (5)% vs 61 (7)% (P<0.01)) (Fig. 1, Table 3).

**Assisted recovery**

Maximum assisted recovery was comparable between groups (27 (7)% vs 32 (6)% respectively; ns). In addition, the maximum effect of neostigmine occurred after 7 (range 5–8) min in patients pretreated with MgSO4 and after 6 (4–10) min in those not exposed to MgSO4 (ns). During the

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first 5 min after the reversal regimen, assisted recovery was less in patients pretreated with MgSO4 compared with controls. After 5 min, the respective values were 23 (8)% and 28 (6)% (P<0.05). However, from 6 to 10 min after reversal, there was no significant difference between the two groups. Values at 10 min were 25 (8)% and 22 (6)% (ns) (Table 4).

Cardiovascular effects

In group B, five patients had episodes of bradycardia. In each patient bradycardia occurred 5–10 min after administration of the reversal agent. In patients pretreated with MgSO4 (group A), four patients had episodes of bradycardia. Bradycardia occurred 6–9 min after administration of the reversal agent.

Discussion

We have investigated for the first time, in a prospective, randomized, double-blind manner, the effect of neostigmine in antagonizing vecuronium-induced neuromuscular block with and without MgSO4 pretreatment. The most important finding was that overall recovery after neostigmine 0.02 mg kg⁻¹ was approximately 30% less in the MgSO4 /vecuronium group compared with the vecuronium group. This was mainly a result of slower spontaneous recovery and not decreased response to neostigmine (Fig. 1, Table 3).

In groups A and B, neostigmine was given at the same degree of recovery of T1 (10%). Thus despite the influence of MgSO4 on the time course of neuromuscular block, the starting point was the same for both groups. Recovery from neuromuscular block was assessed every minute for 10 min after neostigmine administration to allow the peak effect of the drug to occur.17

We chose neostigmine 0.02 mg kg⁻¹ to antagonize neuromuscular block because the cardiovascular side effects of neostigmine are dose-dependent,18 and MgSO4 may also lead to cardiovascular effects. There was no information available on the possible cardiovascular effects of combined use of neostigmine and MgSO4. In addition, it was not our intention to determine the maximum neostigmine-induced recovery which can be obtained in patients treated with vecuronium/MgSO4, but to compare the effect of a standardized dose of neostigmine in this context and to gain insight into the mechanisms leading to delayed recovery. In our study, the effect of neostigmine in antagonizing vecuronium/ MgSO4 neuromuscular block was investigated during isoflurane anaesthesia. Isoflurane potentiates the action of vecuronium and stopping volatile anaesthetic induces some degree of recovery from neuromuscular block.19 However, this is probably not relevant during pharmacologically-induced reversal with neostigmine. McCourt, Mirakhur and Kumar demonstrated that stopping isoflurane at the time of administration of neostigmine did not shorten recovery times after rocuronium.20

When antagonists are used in clinical practice, spontaneous recovery continues at the same time as antagonist-induced recovery takes place. To estimate the contribution of neostigmine in this context, one has to separate the effect produced by the anticholinesterase from spontaneous recovery. This can be done by two different approaches: first, spontaneous recovery from neuromuscular block during antagonism may be eliminated by constant infusion of neuromuscular blockers. In this setting the observed overall recovery depends on the antagonist alone as no spontaneous recovery may occur.21 Second, one can subtract mean spontaneous recovery from actual antagonist-induced recovery, thus calculating assisted recovery.16 The first approach provides information on the effect of the anticholinesterase drug at a given degree of neuromuscular block. However, neostigmine is more efficacious when the intensity of neuromuscular block is less. The potency of anticholinester-
ase drugs is inversely related to the degree of neuromuscular block. We chose the latter method as it takes into account this phenomenon.

Using this approach, we demonstrated that maximum assisted recovery was not different in those patients pretreated with MgSO₄ compared with those not pretreated. In addition, time to maximum effect was also comparable. However, during the initial 5-min period after administration of neostigmine, assisted recovery was less in group A compared with group B. This may be explained by the fact that the dose–effect curve of neostigmine is shifted to the right in the presence of profound neuromuscular block. Thus the slower offset of neuromuscular block in the MgSO₄ pretreated group probably decreased the initial potency of neostigmine.

The findings of our study may have clinical implications. As the response to neostigmine is not the main factor contributing to impaired recovery in patients pretreated with MgSO₄, large or repetitive doses of neostigmine may not further improve reversal. This is supported by the findings of Sinatra and colleagues, describing incomplete recovery from neuromuscular block in a 58-kg pre-eclamptic patient receiving MgSO₄. Reversal with neostigmine 5 mg was attempted. Increased doses of neostigmine may increase the potential for cardiovascular side effects and probably do not further improve overall recovery. One may speculate if calcium may be useful in this context. Calcium entry into the presynaptic nerve terminal is necessary for acetylcholine release, and magnesium competitively blocks calcium entry. Evidence implicating this mechanism includes data from frog nerve and muscle preparations, demonstrating that end-plate potentials evoked by nerve stimulation were reduced in the presence of increased magnesium concentrations and that this could be corrected by adding calcium. Moreover, in a muscle–nerve model, an increasing calcium concentration decreased the sensitivity to tubocurarine and pancuronium, shifting the dose–response curves to the right. Al-Mohaya, Naguib and Abdelatif described a patient with hyperparathyroidism in whom hypercalcaemia was associated with decreased sensitivity to atracurium and

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**Fig 1 Neostigmine-induced recovery: mean first twitch height (T1) vs time after administration of neostigmine. Neostigmine was injected when T1 reached 10%. Spontaneous recovery: mean T1 vs time without administration of neostigmine. Spontaneous recovery of neuromuscular block was assessed when T1 reached 10%. **P<0.01.

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**Table 3 Neostigmine-induced and spontaneous recovery of T1. Recovery was assessed when T1 reached 10%. Within the neostigmine-induced and spontaneous recovery groups, patients treated with MgSO₄ were compared with those not pretreated with MgSO₄. Values are mean (sd). **P<0.01**

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a shortened time course of neuromuscular block. Calcium gluconate caused some improvement in neuromuscular effects related to neostigmine. However, there was no difference between patients pretreated with MgSO4 compared with those not pretreated, suggesting that MgSO4 does not further increase the incidence of cardiovascular effects related to neostigmine.

References

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