

Recovery from neuromuscular block after an intubation dose of cisatracurium and rocuronium in lumbar disc surgery

P. HANS, Ph. WELTER, P. Y. DEWANDRE, J. F. BRICHANT and V. BONHOMME

Summary : *Background and objective :* Residual muscle paralysis remains a concern for anaesthesiologists. This study investigated the recovery from neuromuscular block (NMB) after an intubation dose of cisatracurium (C) or rocuronium (R) in 32 patients undergoing lumbar disc surgery.

Methods : Anaesthesia was induced with propofol and sufentanil, and maintained with sevoflurane in nitrous oxide/oxygen. Patients were randomised to receive twice the ED₉₅ of either cisatracurium (GC) or rocuronium (GR) before tracheal intubation. After placement in prone position, neuromuscular transmission was monitored at the wrist by accelerometry. NMB was antagonised when the TOF ratio (TOFR) was < 0.75 at muscle closure. The time from muscle relaxant to muscle closure, and to TOFR of 0.25 and of 0.50 were recorded. Data were analysed using Student's *t*-tests, chi-squared tests and two-way mixed-designed ANOVA's. The prediction probability (P_k) of the times from muscle relaxant to muscle closure, and to TOFR of 0.25 for the necessity to antagonize NMB was calculated in both groups. $P < 0.05$ was considered statistically significant. *Results :* NMB was antagonized in 8 (GC) and 6 (GR) patients, respectively. The time from muscle relaxant to muscle closure was shorter in patients whose NMB was antagonized. The P_k of this time was significant in GC (0.85) but not in GR (0.69). In GR contrarily to GC, the times to a TOFR of 0.25 and 0.50 were longer in patients whose NMB was antagonized. The P_k of the time to TOFR of 0.25 was significant in GR (0.95) but not in GC (0.64).

Conclusions : A single dose of cisatracurium or rocuronium may be associated to some degree of NMB at the end of lumbar surgery, depending on the duration of surgery and on the duration of action of the muscle relaxant which is more variable for rocuronium than for cisatracurium.

Keywords : Neuromuscular block, muscle relaxants, cisatracurium, rocuronium, monitoring, lumbar disc surgery.

Postoperative residual neuromuscular block (NMB) following the use of muscle relaxants remains an important concern for anaesthetists in so far it may result in morbidity and mortality (2).

For several years, this phenomenon has been thought to be strongly related to the use of long acting muscle relaxants such as pancuronium (2). Indeed, the high incidence of residual paralysis observed in patients who received pancuronium has been shown to be substantially reduced with the use of intermediate-acting muscle relaxants such as atracurium and vecuronium (4, 14). However, postoperative NMB has also been reported to occur with vecuronium, atracurium and rocuronium (1, 13, 16), and even with the short acting muscle relaxant mivacurium (3). In those reports, patients exhibiting postoperative residual NMB, compared to those who did not, were usually given larger doses of muscle relaxants and had significantly shorter time intervals between the administration of the last dose and the administration of the antagonist. In a recent study, residual paralysis has also been detected in the post anaesthesia care unit after a non-reversed single dose of intermediate-duration muscle relaxant (6).

In this prospective study, we examined the intraoperative recovery from NMB after an intubation dose of cisatracurium and rocuronium in patients undergoing routine lumbar disc surgery. We also sought at the predictive factors of potential postoperative residual NMB in those patients.

METHODS

After approval of the Hospital Ethics Committee was obtained, 32 adult ASA status I or II consenting patients scheduled to undergo elective lumbar disc surgery were enrolled in the study. All of them were free of neuromuscular, renal, hepatic

P. HANS, Ph. WELTER, P. Y. DEWANDRE, J. F. BRICHANT and V. BONHOMME

University Department of Anaesthesia & ICM, CHR de la Citadelle, University Hospital, Liege, Belgium

Correspondence address : Professor Pol Hans, University Department of Anaesthesia & ICM, CHR de la Citadelle, Boulevard du 12^{ème} de Ligne 1, B-4000 Liège (Belgium). Phone : 32-4 225 64 70. Fax : 32-4 225 73 08. E-mail : pol.hans@chu.ulg.ac.be

or cardiopulmonary disease and did not receive any medication known to alter neuromuscular transmission. Alcohol and drug addiction were also considered as exclusion criteria.

Patients were premedicated with alprazolam 0.5 mg and atropine 0.5 mg given orally 1 h before surgery. After arriving in the operating room, heart rate, blood pressure and oxygen saturation were monitored continuously. Patients were randomly allocated to one of two groups of 16 patients each to receive twice the ED₉₅ of either cisatracurium (GC: 0.1 mg kg⁻¹) or rocuronium (GR: 0.6 mg kg⁻¹) before tracheal intubation (5, 11). Anaesthesia was induced intravenously with sufentanil 0.15 µg kg⁻¹, ketamine 0.15 mg kg⁻¹ and propofol 2 mg kg⁻¹. After tracheal intubation, anaesthesia was maintained with sevoflurane (1.5 to 2% end tidal) and 60% nitrous oxide in oxygen. After patients were placed in prone position, neuromuscular transmission was monitored at the wrist by accelerometry using the TOF-Guard monitor (Organon Teknika, Biometer International, Odense, Denmark). Stimulation electrodes were placed on the cleaned and rubbed skin over the ulnar nerve close to the wrist, the forearm and the hand being firmly maintained in abduction. Palmar skin temperature was kept above 32 °C throughout the study. The response to Train of Four (TOF) stimulation was assessed at 15-s intervals by stimulation of the ulnar nerve with 4 impulses at 0.5 sec intervals, duration 0.2 ms and 60 mA intensity. It was decided to antagonize NMB using neostigmine combined with atropine when the ratio of the twitch height of the fourth impulse to the height of the first (TOFR) was < 0.75 at muscle closure, i.e. a few minutes before completion of surgery. The anaesthetist in charge of neuromuscular transmission monitoring and NMB reversal was blinded to the muscle relaxant administered. The time from muscle relaxant injection to muscle closure was recorded as the duration of surgery. The times from muscle relaxant injection to the recovery of a TOFR of 0.25 and 0.50 were also recorded.

Data are presented as means (± SD). Statistical analysis was performed using Student's *t*-tests, chi-squared tests and two-way mixed-designed ANOVA's. Normality of distributions was checked when required. The prediction probability (*P_k*) of the times from muscle relaxant injection to muscle closure, indicative of the duration of surgery, and to the recovery of a TOFR of 0.25 for the necessity to antagonize NMB (reflecting a TOFR < 0.75 at muscle closure) was calculated in both groups. *P_k* is a non parametric measure which

has a value of 1 when the indicator (time from muscle relaxant injection to muscle closure and to the recovery of a TOFR of 0.25) predicts the necessity to antagonize NMB (TOFR at muscle closure < 0.75) perfectly, and a value of 0.5 when the indicator predicts no better than a 50:50 chance. Methodology of this statistical analysis has been described in details elsewhere (17). A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Both groups of patients were similar regarding age, weight and body mass index, gender distribution and duration of surgery (table 1). Main results of the study are displayed in table 2.

Table 1

Patient characteristics and duration of surgery.

| [mean(SD) or (n)] | Cis-atracurium (16) | Rocuronium (16) |
|---------------------------|---------------------|-----------------|
| Age (yr) | 42.2 (8.7) | 46.2 (14.9) |
| BMI | 24.2 (3.7) | 25.9 (3.9) |
| Male/female (n) | 9/7 | 11/5 |
| Duration of surgery (min) | 56.3 (18.5) | 65.5 (16.1) |

Table 2

Characteristics of recovery from NMB after twice the ED₉₅ of cisatracurium and rocuronium. Patients were classified into two groups according to their TOFR at muscle closure (< 0.75 or not). TMC: time from muscle relaxant injection to muscle closure. TTR 0.25 = time from muscle relaxant injection to the recovery of a TOFR of 0.25. TTR 0.50 = time from muscle relaxant injection to the recovery of a TOFR of 0.50. *P_k* = the predictive value for the necessity to antagonize NMB.

| [mean(SD) or (n)] | Cis-atracurium (n =16) | | Rocuronium (n =16) | |
|---------------------------|------------------------|------------------|--------------------|------------------|
| | NMB reversed | NMB not reversed | NMB reversed | NMB not reversed |
| Number of patients | 8 | 8 | 6 | 10 |
| TOFR at MC | 0.44 (0.21) | 0.88 (0.11)+ | 0.52 (0.15) | 0.91 (0.09)+ |
| TMC (min.) | 63.8 (14.5) | 87.4 (17.8)+ | 77.5 (13.1) | 88.2 (17.5)+ |
| TTR 0.25 (min.) | 50.1 (12.4) | 49.8 (5.3) | 60.4 (6.5) | 36.1 (15.1)*+ |
| TTR 0.50 (min.) | 61.8 (7.7) 8 | 61.2 (6.2) 6 | 74.4 (11.1)* 10 | 48.9 (17.9)*+ |
| | TTR 0.25 | TMC | TTR 0.25 | TMC |
| <i>P_k</i> (SE) | 0.64 (0.14) | 0.85 (0.09)# | 0.95 (0.07)# | 0.69 (0.14) |

+ = *p* < 0.05 compared to antagonized, * = *p* < 0.05 compared to cisatracurium, # = *p* < 0.05

At muscle closure, 8 patients from GC (50%) and 6 patients from GR (37.5%) had a TOFR < 0.75 and received neostigmine 40 µg.kg⁻¹ intravenously combined with 15 µg kg⁻¹ atropine to antagonize NMB, according to the study protocol. In the global study population, the TOFR at muscle closure was unsurprisingly smaller in patients whose NMB was reversed and the difference was statistically significant (0.48 ± 0.18 vs 0.90 ±

0.09 %, respectively). The duration of surgery, recorded as the time elapsed from muscle relaxant injection to muscle closure, was also significantly shorter in patients whose NMB was reversed (69.6 ± 15.1 vs 87.8 ± 17.0 min, respectively). The P_k of the time from muscle relaxant injection to muscle closure for the necessity to antagonize NMB, reflecting a TOFR < 0.75 at muscle closure, was significant in GC (0.85 ± 0.09 , $p < 0.05$) but not in GR (0.69 ± 0.14 , NS).

The times from muscle relaxant injection to the recovery of a TOFR of 0.25 and 0.50 were longer in patients whose NMB was reversed. Those differences were statistically significant in GR (60.4 ± 6.4 and 74.4 ± 11.9 min vs 36.1 ± 15.1 and 48.9 ± 17.9 min) but not in GC (50.1 ± 12.4 and 61.8 ± 7.7 min vs 49.8 ± 5.3 and 61.2 ± 6.2 min). In Figure 1, the value of the TOFR at muscle closure has been plotted against the time from muscle relaxant injection to the recovery of a TOFR of 0.25. In GC, patients whose NMB was antagonized compared to those whose NMB was not had comparable values of the time to recovery of a TOFR of 0.25 and differed only by the TOFR at muscle closure. In GR, the two categories of patients differed according to the TOFR at muscle closure and also to the time to the recovery of a TOFR of 0.25. Consequently, the P_k of this time for the necessity to antagonize NMB was significant in GR (0.95 ± 0.07) but not in GC (0.64 ± 0.17).

When comparing patients whose NMB was not reversed, the times from muscle relaxant injection to the recovery of a TOFR of 0.25 and 0.50 were significantly shorter in GR (36.1 ± 15.1 , and 48.9 ± 17.9 min) than in GC (49.8 ± 5.3 and 61.2 ± 6.2 min). In contrast, in patients whose NMB was antagonized, the time to achieve a TOFR of 0.50 was significantly longer in GR (74.4 ± 11.9 min) than in GC (61.8 ± 7.7 min).

DISCUSSION

The main finding of this study is that a single intubation dose of either cisatracurium or rocuronium may be associated to some degree of residual NMB at the end of lumbar disc surgery. Indeed, 37.5 to 50% of our patients had a TOF ratio lower than 0.75 at muscle closure. In addition to the time elapsed between the single administration of the muscle relaxant and the end of the surgical procedure, assumed to reflect the duration of surgery, incomplete recovery of neuromuscular function is also depending on the duration of action of the muscle relaxant. This parameter, reflected by the time to recovery of a TOFR of 0.25, was more variable for rocuronium than for cisatracurium.

An obvious methodological limitation of our study is that the calibration of the accelerometer was impossible since neuromuscular transmission was monitored in patients placed in prone position

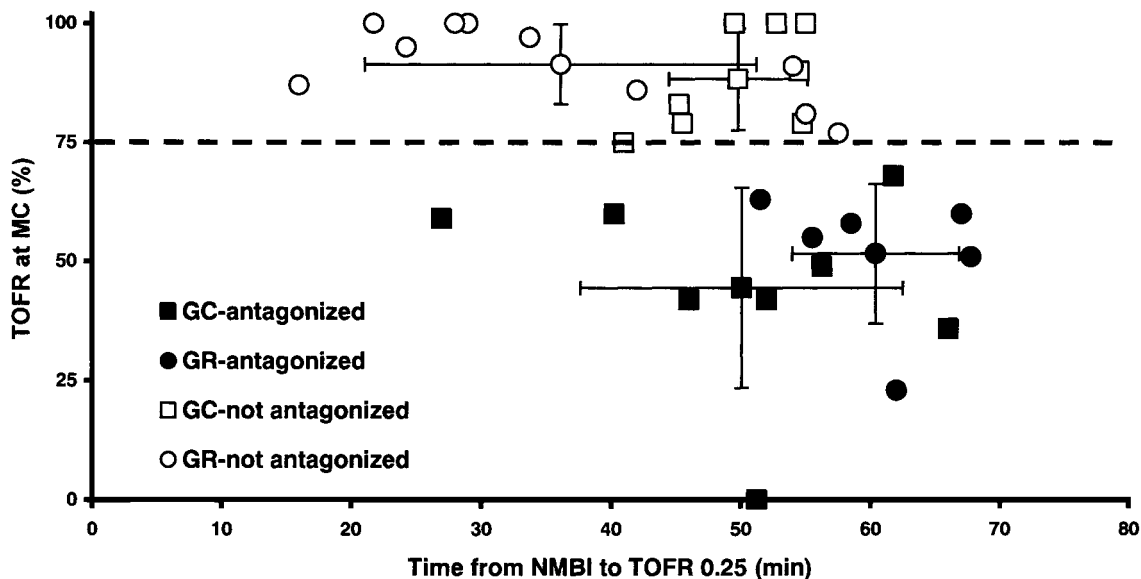


Figure 1. — Scatter plot of time from NMB injection (NMBI) to a TOFR of 0.25 against TOFR at MC. Squares and circles correspond to data obtained in GC and GR patients, respectively. Dark and open symbols refer to NMB reversal and no NMB reversal, respectively. For each set of data, mean values with corresponding SD's are displayed. Discontinued line indicates a TOFR at MC of 0.75. In GC, patients whose NMB was antagonized and those who did not required reversal had comparable average time to a TOFR of 0.25 but differed according to the time from muscle relaxant to muscle closure. In GR, the two categories of patients differed both according to the time from muscle relaxant to muscle closure and to the time to a TOFR of 0.25.

after induction of anaesthesia. However, such a calibration before injection of the muscle relaxant is not mandatory for clinical use and the study was designed to address a safety issue in clinical practice. Therefore, we assessed the response to 60 mA TOF stimulation of the ulnar nerve using accelerometry which has been proven suitable in routine practice and allows quantitative measurement of NMB. Likewise, using the TOF-ratio to assess neuromuscular transmission does not require a control value before muscle relaxant injection. Accelerometry has already been used to detect residual NMB and has been shown to be more efficient than clinical evaluation in that purpose (12).

In this study, the number of patients with a TOFR of 0.75 or more at muscle closure was higher in GR (10 patients) than in GC (8 patients), but the difference was not significant ($\chi^2_{(1)} = 0.508$, $p = 0.476$; power = 0.94 assuming that a proportion of patients with a TOFR lower or higher than 0.75 at muscle closure of 50/50 in one group and 70/30 in the other group is a clinically relevant difference). The important message is that a single intubation dose of each muscle relaxant may be associated with an incomplete recovery of neuromuscular function at the end of surgery. Patients with a TOFR < 0.75 at muscle closure, i.e. a few minutes before completion of surgery, may be considered at risk for postoperative residual NMB. A TOFR of 0.75 was chosen because it has been considered for many years as reflecting safe recovery of neuromuscular function. However, this value is no longer acceptable today. Indeed, a TOFR greater than 0.90 at the adductor pollicis is necessary to eliminate any significant influence of residual paralysis on hypoxic ventilatory control, to store normal pharyngeal function and avoid an increased risk for pulmonary aspiration (8-10, 18). Volunteers subjected to partial paralysis feel uncomfortable at TOFR < 0.75 and still report visual disturbances at TOFR < 0.90 (15). Recently, it has been shown in volunteers partially paralysed that impaired inspiratory flow and upper airway obstruction frequently occur at a TOFR of 0.8 and that respiratory function can still be impaired at a TOFR of unity (7).

Postoperative residual NMB reflects an imbalance between the time elapsed between the last administration of the muscle relaxant and the end of surgery, and the duration of action of the muscle relaxant. In a study investigating postoperative residual NMB with the use of atracurium, the duration of surgery has been reported to be the sole multivariate predictor of residual NMB among different possible contributing factors (16). In this

study, the time between injection of either cisatracurium or rocuronium and muscle closure was significantly shorter in patients whose the TOFR was < 0.75 at this endpoint. However the predictive value of this parameter for the necessity to reverse NMB was significant in GC but did not reach the level of statistical significance in GR. As it was decided to reverse NMB when the TOFR was < 0.75 at muscle closure, this difference between the two groups is likely explained by a different pattern of recovery from NMB between the two muscle relaxants. Indeed, a single injection of a muscle relaxant may be hazardous when its duration of action is longer than the expected duration of the surgical procedure. In the present study, the times elapsed from cisatracurium administration to the recovery of a TOFR of 0.25 and 0.50 were comparable in all patients whatever NMB was antagonized or not. In contrast, in the rocuronium group, those time intervals were significantly longer in patients whose NMB was reversed. Comparing patients whose NMB was reversed in both groups, the time to recover a TOFR of 0.50 was also significantly longer in GR than in GC. Those results are consistent with a more variable duration of action of rocuronium compared to cisatracurium. Hence, the predictive value of the time to achieve a TOFR of 0.25 for the necessity to reverse NMB was statistically significant in patients who received rocuronium but not cisatracurium. As already stressed, the time to achieve a TOF ratio of 0.25 reflects the duration of action of the muscle relaxant and should not be considered per se as a predictive factor for the necessity to reverse NMB in clinical practice. The use of halogenated volatile anaesthetics may account for the observed pharmacodynamic variability of rocuronium which has already been reported in the literature (19). This variability is clearly illustrated in figure 1, where the time from NMB injection to TOFR 0.25 has been plotted against the TOFR at muscle closure. In GC, the average time to recover a TOFR of 0.25 was comparable in the two subgroups of patients, whatever the TOFR at muscle closure was lower or higher than 0.75 and NMB was antagonized or not. In GR, this time was significantly longer in patients who had a TOFR < 0.75 at muscle closure and whose NMB was antagonized.

In conclusion, a single intubation dose of either cisatracurium or rocuronium may be associated to some degree of residual NMB at the end of lumbar disc surgery. Consequently, absence of appropriate antagonism might result in postoperative residual NMB. Incomplete recovery of neuro-

muscular function depends on the duration of surgery, or more accurately on the time elapsed between the last administration of the muscle relaxant and the end of the surgical procedure, and on the duration of action of the muscle relaxant which was more variable for rocuronium than for cisatracurium under sevoflurane anaesthesia. Those results strongly support a systematic use of neuromuscular transmission monitoring even after a single dose of an intermediate-acting muscle relaxant.

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