J Anesth (1997) 11:245–249

Journal of
Anesthesia

Original articles

Comparison of sensitivity of neuromuscular monitoring tests: twitch versus tetanic test

MUKESH TRIPATHI, PRABHAT K. SINGH, SUSHIL P. AMBESH, and SOMA KAUSHIK

Department of Anaesthesiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Pin-226 014, India

Abstract

Purpose. The study was planned to compare the sensitivity of a twitch neuromuscular monitoring test, the train-of-four (TOF), with a tetanic test, double-burst stimulation (DBS), during a subclinical dose of vecuronium.

Methods. Twenty consenting. ASA I patients (16 to 65 years of age) of both sexes were studied. The ulnar nerve was stimulated at the wrist through surface electrodes by Myotest-DBS, and the adductor pollicis response was recorded on Myograph-2000. After stabilization of the twitch tension at titrated supramaximal stimuli (1 Hz), patients were randomly allocated into groups. In group 1 (n = 10), the TOF test was monitored; in group 2 (n = 10), the DBS test was monitoral. All patients received a priming dose of vecuronium (0.015 mg·kg^{-1}); parameters such as T_1 and TOF ratio (TOFr) (T_4/T_1) were noted in group 1, and D_1 and DBS ratio (DBSr) (D_2/D_1) were noted during the vecuronium effect.

Results. The DBS test showed a wider range of change (from control 1.00 to 0.62 ± 0.19 for D_1 and to 0.37 ± 0.14 for DBSr) at a faster rate (0.07 ± 0.04 min^{-1} for D_1 and 0.08 ± 0.02 min^{-1} for DBSr) during the block progression phase than the TOF test parameters (T_1 and TOFr). The tetanic fade or DBSr showed peak onset later than peak twitch suppression. The rate of recovery of the DBS test was also slower than that of the TOF test after the peak effect.

Conclusions. DBS is a more sensitive test than TOF to quantify the subclinical dose effect of vecuronium, and among the studied parameters (T_1, TOFr, D_1 and DBSr), DBSr, measuring tetanic fade, was the most sensitive single parameter.

Key words: Neuromuscular monitoring, Train-of-four, Double-Burst Stimulation, Vecuronium

Address correspondence to: M. Tripathi

Received for publication on October 3, 1996; accepted on May 10, 1997

Introduction

Neuromuscular junction (NMJ) monitoring with non-depolarizing neuromuscular blocking agents (NMBA) has shown a variable onset time, depending upon the frequency of stimuli used [1]. The train-of-four (TOF) is reported to be more sensitive, with a quicker onset time for the same NMBA dose effect than the single twitch (1 Hz) [2,3]. Further, the tetanic test (50 Hz for 1 s) also showed quicker onset than 1 Hz stimuli [4]. The reversal of tetanic fade during NMBA is taken as the most sensitive index to assess residual non-depolarizing neuromuscular block (NMB) [3–5]. However, during conventional tetanic stimuli (50 Hz for 1 s), tetanic fade estimation is difficult. In the tetanic-type double-burst stimulation (DBS) test [6], tetanic fade can be measured by calculating the DBS ratio (DBSr) (D_2/D_1) in a clinical setting.

Since the intubation dose of vecuronium causes complete cessation of the adductor pollicis response for a variable period of time, it is not possible precisely to estimate the peak suppression of the stimulus response or its onset time. Considering this limitation, it was planned to use subclinical (priming) dose of vecuronium, which does not lead to 0 response state during clinical NMJ monitoring. The aim of this study was to compare the a sensitivity of the DBS test and the TOF test in quantifying the subclinical or priming dose effect of vecuronium.

Materials and methods

Twenty patients, ASA physical status I, ranging in age from 16 to 65 years and scheduled for general anesthesia for routine surgery, were selected for the study. The study protocol was approved by our institute's ethical committee for clinical investigations. Prior informed consent was obtained from all patients. Patients with a

history of medication known to interact with NMBA or with neuromuscular disorders were excluded from the study.

All patients were premedicated with intramuscular buprenorphine (0.005 mg·kg^{-1}) 1 h before surgery. In the operating room, NMJ monitoring was done by stimulating the ulnar nerve at the wrist by surface electrodes using Myotest-DBS. A 250- to 300-g pretension was maintained at the thumb, and the adductor response was recorded using a force-displacement transducer on Myograph-2000 (Biometer, Denmark). Twitch tension was stabilized at the titrated supramaximal, square-wave stimulus of 0.2 ms width at 1 Hz.

Patients were randomly assigned to two groups. In group 1 ($n = 10$) patients, the TOF (four stimuli at 2 Hz) test, repeated at 12 s, was monitored to note T_1 height and TOF ratio (T_4/T_1). In group 2 ($n = 10$) patients, after stabilization of the twitch response at supramaximal stimuli, the DBS test (burst of three stimuli each at 50 Hz and at a gap of 750 ms) was monitored. As the D_1 height exceeded 2.5 to 3 times the twitch response, the amplitude gain was readjusted to get D_1 at 1.00. With each DBS stimulus, repeated at 20-s intervals, DBSr (D_2/D_1) was calculated by a Casio calculator (Fx-100). The effect of the priming dose of intravenous vecuronium (0.015 mg·kg^{-1}) was monitored in awake patients for 15 min.

We recorded the lag time (from the time of vecuronium injection to observed suppression of T_1 in TOF or D_1 in DBS), peak T_1, TOFr, D_1, and DBSr suppression with respective onset times and the recovery trend up to 15 min after vecuronium injection. To assess the sensitivity of the monitored tests in quantifying identical doses of vecuronium, the range of peak fall, rate of decline, and rate of recovery of different parameters were calculated and compared. We also observed the appearance and duration of any paretic side effects i.e., diplopia; difficulty in opening the eyes, lifting the head, or protruding the tongue; heaviness over the chest, or breathing difficulty and the NMJ block. ECG lead II, arterial blood pressure, and pulse oximetry were monitored in the standard manner. Oxygen was given through a face mask and expiratory tidal volume was monitored by a Wright spirometer.

Values are given as mean ± SD. One-way analysis of variance (ANOVA) was used to compare the results from the two groups of patients. $P < 0.05$ was taken as statistically significant.

Results

Patients in both groups were similar in age, sex, and weight (Table 1). Typical myographs recorded in patients of the two groups are illustrated in Fig. 1. The vecuronium (0.015 mg·kg^{-1}) effect as measured by the TOF and DBS test at 1, 2, 3, 4, 5, 7, 10, 13, and 15 min are shown in Table 2 along with the trend graph in Fig. 2. All four parameters (T_1, TOFr, D_1, and DBSr) showed significant ($P < 0.01$) changes in response to vecuronium.

The DBS test had a shorter lag time (92 ± 32.95 s) than the TOF test (108 + 21.0 s). Tetanic fading (DBSr) had significantly ($P < 0.05$) greater suppression (from 1.00 to 0.37 ± 0.14) and quicker onset time (456 ± 56.4 s) than TOFr in the TOF test. After 15 min of vecuronium, DBSr (0.69 ± 0.17) still showed significant ($P < 0.05$) suppression from its control as compared with TOFr. The fading response TOFr and DBSr in both the tests showed significantly ($P < 0.05$) delayed peak suppression onset as compared with the respective T_1 in the TOF test and D_1 in the DBS test, peak twitch suppression time (Table 3).

Table 1. Demographic data on patients

Characteristic	Group 1	Group 2
Neuromuscular test	Train of four (TOF)	Double-burst stimulation (DBS)
Age (mean ± SD) (yr)	40 ± 13	41 ± 14
Range	(22–58)	(18–65)
Weight (mean ± SD) (kg)	64 ± 11	58 ± 15
Range	(51–84)	(35–87)
Male : female	6:4	5:5

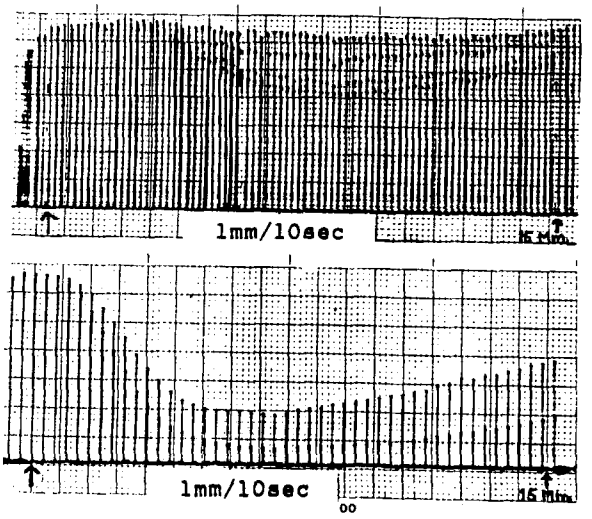

Fig. 1. Typical trace of myographs recorded for the subclinical dose effect of vecuronium in two groups. *Upper end dots* represent number of stimuli given with each stimulus, i.e., 4 in train of four (**A**) and 2 in double-burst stimuli (**B**). *Arrow* shows point of vecuronium injection

Table 2. Effect of priming dose of vecuronium as monitored by TOF and DBS tests (mean ± SD)

	Group 1		Group 2	
Time	T_1*	TOFr*	D_1*	DBSr*
Control (predrug)	1.00	1.00	1.00	1.00
After drug (min)				
1	0.97 ± 0.05	0.96 ± 0.07	0.99 ± 0.07	0.99 ± 0.014
2	0.93 ± 0.07	0.89 ± 0.06	0.94 ± 0.07	0.96 ± 0.04
3	0.85 ± 0.15	0.83 ± 0.13	0.84 ± 0.18	0.86 ± 0.11
4	0.79 ± 0.17	0.80 ± 0.17	0.72 ± 0.25	0.69 ± 0.17
5	0.75 ± 0.20	0.74 ± 0.21	0.67 ± 0.27	0.54 ± 0.15
7	0.75 ± 0.22	0.67 ± 0.23	0.61 ± 0.26	0.43 ± 0.13
10	0.77 ± 0.20	0.62 ± 0.22	0.65 ± 0.25	0.44 ± 0.19
13	0.88 ± 0.09	0.78 ± 0.09	0.74 ± 0.25	0.59 ± 0.20
15	0.94 ± 0.06	0.87 ± 0.07	0.82 ± 0.23	0.69 ± 0.17

* Statistically significant ($P < 0.05$) change after drug.
T_1, Twitch height in train of four test; TOFr, TOF ratio (T_4/T_1); D_1, twitch height in double-burst stimulation test; DBSr, DBS ratio (D_2/D_1).

Table 3. Observations of the patients in the two groups (mean ± SD)

Observation	Group 1 (TOF)	Group 2 (DBS)
Lag time (s)	108.2 ± 21.0	92.0 ± 32.92
Peak changes in two tests		
Twitch height	T_1	D_1
	0.74 ± 0.23	0.62 ± 0.19
Ratio changes	TOFr	DBSr
	0.60 ± 0.23	0.37 ± 0.142*
Onset time for peak change		
In twitch height (s)	350.8 ± 84.8**	330.0 ± 62.0**
In ratio (s)	501.6 ± 116.0	456.0 ± 56.4*
Recovery 15 min after drug		
In twitch height	T_1	D_1
	0.94 ± 0.06	0.82 ± 0.22
In ratio	TOFr	DBSr
	0.85 ± 0.06	0.69 ± 0.172*

* Significant ($P < 0.05$) difference from group 1.
** Significant ($P < 0.05$) difference from the onset time of respective group ratio change.

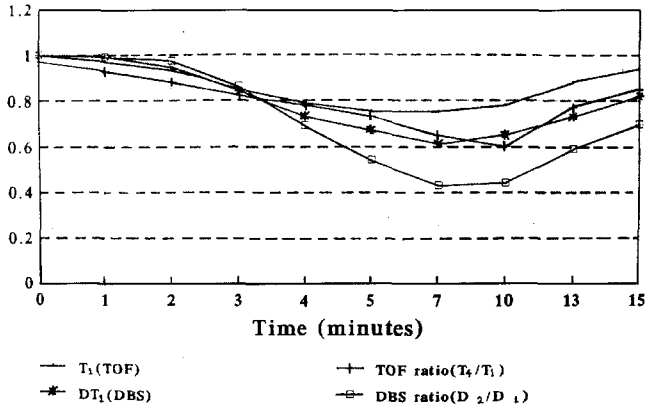

Fig. 2. Graphic representation of trend of changes in T_1, TOF ratio, D_1, and DBS ratio during vecuronium (0.015 mg·kg^{21})

In terms of three sensitivity indices, DBS showed a significantly ($P < 0.05$) wider range of change in DBSr (0.63 ± 0.15) than in TOFr (0.43 ± 0.24). The rate of decline in DBSr (0.08 ± 0.02 min^{-1}) was significantly ($P < 0.01$) more rapid than any other parameter (T_1, TOFr, or D_1) in the block progression phase. After the peak effect, the DBS test (D_1 and DBSr) had a nonsignificantly ($P > 0.05$) slower recovery rate than the TOF test (T_1 and TOFr) (Table 4).

Patients developing paretic symptoms during the priming dose effect were comparable in both the groups (Table 5). The paretic ocular symptoms started 1.2 ± 0.2 min after the priming dose and lasted 3.5 ± 1.2 min, which is well behind the peak onset time of the TOF or DBS tests at the adductor pollicis.

Table 4. Different sensitive indices of the different monitored parameters from control value of 1.00 (mean ± SD)

	Group 1		Group 2	
Index	T_1	TOF ratio	D_1	DBS ratio
Peak fall	0.24 ± 0.22	0.43 ± 0.24	0.41 ± 0.24	0.63 ± 0.15*
Rate of fall in block Progression (min^{-1})	0.055 ± 0.04	0.054 ± 0.03	0.07 ± 0.04*	0.08 ± 0.02*
Rate of recovery in block regression (min^{-1})	0.025 ± 0.02	0.05 ± 0.03	0.025 ± 0.009	0.04 ± 0.009

*Significant ($P < 0.05$) difference from comparable parameter.

Table 5. Incidence of various clinical symptoms observed during priming. Number of patients (%)

Symptom	Group 1	Group 2
Diplopia	7 (70.0)	7 (70.0)
Drooping of eyelids	5 (50.0)	4 (11.0)
Difficulty in swallowing	2 (20.0)	1 (10.0)
Heaviness in chest	2 (20.0)	3 (30.0)
Difficulty in tongue protrusion	1 (10.0)	—
Hypoventilation (tidal volume < 4 ml·kg^{-1})	—	—

Discussion

The results showed that for identical vecuronium, the DBS test parameters (D_1 and DBSr) had a greater degree of change at a faster rate than the TOF test parameters (T_1 and TOFr). During block regression, the DBS test showed a slower recovery than the TOF test, and 15 min after vecuronium injection, the DBS parameters still showed a significant degree of block as compared with the TOF parameters.

Payne and Hughes [4] have reported that during NMB, tetanic stimuli (50 Hz for 1 s) showed amplitude suppression and terminal fading. They also reported that when tetanic and twitch stimuli (1 Hz) were monitored simultaneously in two hands of the same patient during atracurium block, the tetanic test had quicker onset and slower recovery than the twitch (1 Hz) test. It was thought to be due to a higher degree of stress by the tetanic test [4]. Since DBS is a similar variant of the tetanic test, consisting of two bursts of three stimuli each at 50 Hz given at intervals of 750 ms, it showed a wider degree of change, with quicker peak onset time and slower recovery than TOF test.

It was noteworthy that the fade, monitored as TOFr or DBSr, was the dominant effect of the priming dose, and its peak onset time distinctly exceeded by more than 1 min the peak onset time of twitch suppression (T_1 or D_1) in both tests. Recently, Huemer and associates [7] in their pharmacodynamic study reported that during vecuronium priming (0.015 mg·kg^{-1}), TOFr still showed suppression when drug plasma levels were below the reported threshold levels [8]. Since 1-Hz stimuli were used for calculating plasma threshold levels of vecuronium in blood [8], it was noticed that the fading continued even beyond peak twitch suppression. We could not measure the plasma levels of vecuronium at our centre, but since we also used a similar dose of vecuronium, our observations of the predominant fading effects, measured as TOFr in the TOF test and DBSr in the DBS test, lasting even beyond the point of peak T_1 or D_1 suppression, are comparable with their study [7].

Moreover, fading of repeated stimuli has been correlated with the extent of acetylcholine (ACh) receptor blockade by NMBA [1,9] and maximum twitch suppression with its peak free drug level at the NMJ [10]. Taking these facts into consideration, it can also be hypothesized that at the state of equilibrium and the peak drug level at the NMJ, because of high affinity, continued drug binding with ACh receptors is likely to result in a net fall in free drug level and a recovery in twitch height but continued fading and therefore delayed peak fading after peak twitch height suppression.

The incidence of side effects due to vecuronium priming (0.015 mg·kg^{-1}) is comparable with that of other studies [11,12]. In our study, however, it was interesting to observe that the ocular or respiratory symptoms in sensitive patients appeared 1 min after drug injection and improved when the peak effect of the priming dose (peak suppression of parameters in both tests) was noted at the adductor pollicis. Therefore, paretic symptoms did not correlate with the peak effect of the vecuronium, monitored at the adductor pollicis.

The centrally well-perfused, smaller, rapidly acting muscles of the eye and respiration [13,14] develoted a higher degree of NMJ block, probably with the acute rise in vecuronium level in the central compartment after bolus injection, when a lesser degree of NMB was

monitored at the adductor pollicis. Later during the phase of drug redistribution, the central muscles became relatively free from the NMBA effect and showed symptomatic improvement, when the peak effect was monitored at the adductor pollicis. Side effects dependent on the rate of injection have also been reported with other drugs, e.g., apnea and hypotension associated with thiopentone [15] and propofol [16] and histamine release associated with atracurium [17]. Thus, we presume that the side effects of bolus priming are also dependent on the rate of injection and are an indicator neither of peak effect nor of hypersensitivity to vecuronium.

In conclusion, we would like to emphasize that the calculated DBSr, measuring tetanic fade, is clinically feasible and is more sensitive than the TOF test to monitor subparalytic (priming) NMB by vecuronium. Side effects during priming are related to the rate of injection (bolus) of the drug.

Acknowledgments. The authors wish to thank Prof. Shimada for his valuable suggestions.

References

1. Ali HH, Utting JE, Grey C (1970) Stimulus frequency in the detection of neuromuscular junction block in humans. Br J Anaesth 42:967–978
2. Curren MJ, Donati F, Bevan DR (1987) Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. Br J Anaesth 59:989–994
3. d'Hollander HA, Duvaldestein P, Delcroix C, Nevelsteen M, Desmonts JM (1982) Evolution of single twitch and train-of-four response and of tetanic fade in relation to plasma concentrations of fazadinium in man. Anesth Analg 61:225–230
4. Payne JP, Hughes R (1981) Evaluation of atracurium in anaesthetized man. Br J Anaesth 53:45–53
5. Waud BE, Waud DR (1971) The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. Anesthesiology 35:456–464
6. Engbaek J, Ostergaard D, Viby-Mogensen J (1989) Double burst stimulation (DBS). A new pattern of nerve stimulation to identify residual curarization. Br J Anaesth 62:274–278
7. Huemer G, Schwarz S, Gilly H (1995) Pharmacodynamics, pharmacokinetics, and intubation condition after priming with three different doses of vecuronium. Anesth Analg 80:538–542
8. Hennis PJ, Stanski DR (1985) Pharmacokinetic and pharmacodynamic factors that govern the clinical use of muscle relaxants. Semin Anesth 4:21–30
9. Bowman WCV (1980) Prejunctional and postjunctional cholinoceptors and the neuromuscular junction. Anesth Analg 59:935–945
10. Epstein RH, Bartkwoski RR (1992) Prediction of vecuronium block onset and time to maximum twitch depression: modification of the Sheiner-Stanski model of the neuromuscular junction. Anesthesiology [suppl] 77:A–443
11. Taboada JA, Rupp SM, Miller RD (1986) Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology 64:243–247
12. Baumgarten RK, Carter CE, Reynolds WJ, Brown JL, De Vera HV (1988) Priming with nondepolarizing relaxants for rapid tracheal intubation: a double-blind evaluation. Can J Anaesth 35:5–11
13. Stoelting RK (1987) Neuromuscular blocking drugs. In: eds Pharmacology and physiology in anesthetic practice. 2nd ed. JB Lippincott, Philadelphia, p 170
14. Chauvin M, Lebreault C, Duvaldestin P (1987) The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 66:117–122
15. Barron DW (1968) Effect of rate of injection on incidence of side effects with thiopentone and methohexital. Anesth Analg 48:174–176
16. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K (1987) Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous-oxide anaesthesia. Br J Anaesth 59:954–960
17. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M (1983) Histamine releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. Br J Anaesth 55:105S–106S