Assessment of double-burst monitoring at 10 mA above threshold current

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We compared fade measurements in response to double-burst stimulation (DBS) at 10 mA above the threshold for the second response (D_2) to that for DBS at 60 mA in order to determine the utility of low-current DBS testing. In 20 healthy adults undergoing general endotracheal anaesthesia with isoflurane 0.5–1% end-tidal, a vecuronium infusion ($0.25\text{--}1.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was delivered until a stable train-of-four (TOF) response to ulnar nerve stimulation was documented with an adductor pollicis force transducer. Then DBS responses were recorded, and the D_2/D_1 ratios were determined at 60 mA and at 10 mA above the D_2 threshold current ($TS + 10\text{ mA}$). The mean difference (bias) between D_2/D_1 @ $TS+10\text{ mA}$ and D_2/D_1 @ 60 mA was -0.02 ($P < 0.05$); the 95% limits of agreement were from -0.12 to $+0.08$. The bias and limits of agreement were similar to those for T_4/T_1 of train-of-four. A strong correlation was noted between the degrees of fade determined at the low and high currents ($r = 0.95$). We conclude that, although stimulation at 10 mA above the D_2 threshold is associated with a slight negative bias, it is virtually interchangeable with testing at higher current in the clinical setting. This technique thus may be used effectively to monitor neuromuscular fade in settings where neurostimulation with low current is deemed desirable.

Nous avons comparé l'affaiblissement (fade) du signal de la deuxième réponse (D_2) du double burst (DBS) mesurée à 10

mA au-dessus du seuil d'excitabilité (TS) à celui du DBS à 60 mA, dans le but de déterminer la validité du test de DBS à basse intensité. L'étude est réalisée chez 20 patients adultes non tarés sous anesthésie générale endotrachéale à l'isoflurane à la concentration télé-expiratoire de 0,5 à 1%. Une solution de vécuronium ($0,25\text{--}1,5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) est perfusée jusqu'à l'obtention d'une réponse stable du cubital au train de quatre. La force de l'adducteur du pouce est établie à l'aide d'un transducteur. Par la suite, on enregistre la réponse au DBS, et le rapport D_2/D_1 est déterminé à 60 mA et à 10 mA au-dessus du seuil ($TS + 10\text{ mA}$). La différence moyenne (biais) entre D_2/D_1 @ $TS+10\text{ mA}$ et D_2/D_1 @ 60 mA est de $-0,2$ ($P < 0,05$); les limites d'accord sont de $-0,12$ à $+0,08$. Le biais et les limites d'accord sont semblables à ceux du train de quatre. On trouve une forte corrélation entre les degrés d'affaiblissement déterminés à des courants de basse intensité avec ceux de haute intensité ($r = 0,95$). Nous concluons que bien que la stimulation à 10 mA au dessus du seuil de D_2 puisse montrer un léger biais négatif, il est superposable à celui qu'on voit avec des courants de haute intensité en clinique. Cette technique peut donc être utilisée efficacement pour mesurer l'affaiblissement de la réponse dans des conditions où un courant de faible intensité est préférable.

Key words

MONITORING: neuromuscular function;
NEUROMUSCULAR RELAXANTS: vecuronium, measurement of response.

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The present study was designed to determine if testing at 10 mA above the threshold of the second stimulus (D_2) of double-burst stimulation (DBS) provided a reliable measure of neuromuscular fade. Several investigators have reported that DBS-induced fade is visualized more readily than is the fade induced by train-of-four (TOF) stimulation, at submaximal¹ as well as supra-maximal¹⁻⁶ stimulating currents. It has been reported recently that stimulation with low current produces less discomfort to awake volunteers than testing with supra-maximal current.⁷ This finding may be particularly beneficial in settings in which patients are awake, such as the post-anaesthesia care unit (PACU) and the intensive care unit (ICU). There is a relatively high incidence of residual block in PACU patients.⁸⁻¹³ The potential for adverse outcome may be even greater in the ICU, in view of the reported persistent block after long-term infusions

of neuromuscular blocking drugs in patients with organ failure.¹⁴⁻²⁰ This has led to the conclusion that "an objective method must be used to assess the depth of neuromuscular blockade whenever nondepolarizing neuromuscular relaxants are administered repeatedly or by infusion in ICU's."¹⁹ However, PACU and ICU staff may be hesitant to test awake patients because of the associated discomfort. This has led to our previous recommendation of low-current testing.^{1,7,10,21-23}

Alternatively, concerns have been raised that testing at low current may distort monitoring indices.^{24,25} These concerns have been addressed for TOF by stimulating at 10 mA above the current which is required to elicit the T_4 (fourth twitch) response.²² Although it was our impression that DBS and TOF would demonstrate similar consistency, the muscle response to mini-tetanic stimuli differs from responses to individual single twitches; the inter-current consistency therefore remains to be confirmed.

Methods

With approval of the institutional Human Investigation Committee, 20 consenting patients (ASA 1-3) undergoing general endotracheal anaesthesia for elective surgical procedures were studied. Patients were between 35 and 70 yr, were within 50% of ideal body weight and were free of known neuromuscular disease. Preinduction medication consisted of fentanyl ($1-3 \mu\text{g} \cdot \text{kg}^{-1}$) and midazolam ($0.01-0.04 \text{ mg} \cdot \text{kg}^{-1}$) *iv*. Cutaneous electrodes (Cleartrace ECG Electrodes, Medtronic, Inc., Haverhill, MA) of a DualStim III nerve stimulator (LifeTech, Inc., Houston, TX) were applied to the arm opposite the blood pressure cuff, with the positive electrode over the proximal, and the negative electrode over the distal, volar forearm. The ipsilateral thumb was abducted with a preload of 300 g in an adductor pollicis force transducer (Myotrace APM, LifeTech, Inc., Houston, TX) interfaced to a monitor and stripchart recorder (2000 A/2000 RS, Datascop Corp., Paramus, NJ).

Anaesthesia was induced with thiopentone ($4-6 \text{ mg} \cdot \text{kg}^{-1}$), and baseline responses to the T_1 and T_4 impulses of TOF and the D_1 and D_2 impulses of DBS were recorded. Then, tracheal intubation was facilitated with succinylcholine ($1 \text{ mg} \cdot \text{kg}^{-1}$) *iv*, and anaesthesia was maintained with isoflurane ($0.5-1.0\%$ end-tidal) and 66% nitrous oxide in oxygen. After recovery from succinylcholine, a bolus dose of vecuronium ($5-50 \mu\text{g} \cdot \text{kg}^{-1}$) was administered, and a continuous vecuronium infusion was started at $0.25-1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to provide a range of TOF ratios.

The study period was initiated when the TOF ratio exhibited a change of less than 5% over a 10-min period. It consisted of three DBS determinations: at 60 mA, at

10 mA above the threshold stimulus ($\text{TS} + 10 \text{ mA}$) for D_2 , and again at 60 mA. The threshold current was determined by increasing stimulator's output in 2-3 mA increments (while DBS was repeated at 20-sec intervals) until D_2 was apparent on the interfaced monitor screen. The DBS ratio at $\text{TS} + 10 \text{ mA}$ was termed $D_2/D_1 @ \text{TS} + 10 \text{ mA}$. The mean of the two determinations at 60 mA provided $D_2/D_1 @ 60 \text{ mA}$. The monitor was zeroed before each neurostimulation to ensure a constant baseline, and thumb abduction was adjusted to maintain a constant preload. For each neurostimulation, the height of the evoked response was estimated to the nearest 0.5 mm by freezing the tracing on the monitor screen and adjusting the built-in monitor reference line in 1-mm increments. From these values, D_2/D_1 ratios were calculated. If surgical time permitted, the vecuronium infusion was adjusted to achieve a different stable degree of neuromuscular block. Then, a second independent set of D_2/D_1 readings was obtained, such that a total of 39 studies was performed.

The overall difference between $D_2/D_1 @ \text{TS} + 10 \text{ mA}$ and $D_2/D_1 @ 60 \text{ mA}$ was analyzed with paired *t* test. A value of $P < 0.05$ was considered statistically important. A scattergram was generated to delineate the relationship between the ratios obtained at low and high currents; this relationship was analyzed with Spearman's assessment of correlation. In addition, agreement between low- and high-current values was assessed according to the method proposed by Bland and Altman:²⁶ the difference between $D_2/D_1 @ \text{TS} + 10 \text{ mA}$ and $D_2/D_1 @ 60 \text{ mA}$ values was displayed graphically, and the overall difference was defined as the mean bias; $2 \times$ the overall standard deviation (SD) of the bias provided the 95% limits of agreement.

To facilitate comparison of the present data with those obtained previously for TOF using accelerography²³ and force translation,^{10,22,28} a set of T_4/T_1 assessments was obtained with each set of D_2/D_1 assessments.

Results

As expected, the amplitudes of the evoked responses were markedly lower at $\text{TS} + 10 \text{ mA}$ than at 60 mA; however, the D_2/D_1 ratios differed only slightly. The mean D_2 threshold current was $17.1 \pm 6.8 \text{ mA}$ (with a range of 8.8-35.2 mA). At 10 mA above this current, the heights of D_1 and D_2 were $18.6 \pm 9.6 \text{ mm}$ and $8.2 \pm 8.7 \text{ mm}$, while the mean D_2/D_1 ratio was 0.40 ± 0.2 . At a current of 60 mA, the mean ($\pm$ SD) magnitudes of D_1 and D_2 were $28.9 \pm 14.5 \text{ mm}$ and $12.6 \pm 10.6 \text{ mm}$, respectively, and the D_2/D_1 ratio was 0.42 ± 0.2 . The differences (bias) between the low and high current testing within individual subjects averaged -10.3 mm (45%) for D_1 ($P < 0.05$ by paired *t* test), -4.4 mm (46%) for D_2 ($P < 0.05$), and -0.02 (5%) for D_2/D_1 ($P < 0.05$).

FIGURE 1 Scattergram of D_2/D_1 @TS+10 mA vs D_2/D_1 @60 mA; $r = 0.95$ by Spearman's assessment of correlation.

FIGURE 3 Scattergram of T_4/T_1 @TS+10 mA vs T_4/T_1 @60 mA; $r = 0.94$ by Spearman's assessment of correlation.

FIGURE 2 Plot of difference between D_2/D_1 @TS+10 mA and D_2/D_1 @60 mA vs their mean value for each data set. Solid line represents mean overall bias (-0.02). Dashed lines represent twice the standard deviation of the bias (i.e., the 95% limits of agreement).

FIGURE 4 Plot of difference between T_4/T_1 @TS+10 mA and T_4/T_1 @60 mA vs. their mean value for each data set. Solid line represents mean overall bias (-0.04). Dashed lines represent twice the standard deviation of the bias (i.e., the 95% limits of agreement).

The scattergram illustrates the strong correlation between the fade at low and high currents ($r = 0.95$, Figure 1). The plot of the difference between the fade ratios obtained at the two currents (y-axis) and their average value (x-axis) demonstrates the close agreement between D_2/D_1 @TS+10 mA and D_2/D_1 @60 mA (Figure 2). The mean bias was -0.02 ; 95% limits of agreement encompassed inter-current differences between -0.12 and $+0.08$. These values were similar to those for the intra-current

comparison at 60 mA, where the mean intra-current difference was 0.01 , and the 95% limits of intra-current agreement were -0.09 to $+0.11$.

The mean T_4 threshold current was 24.4 ± 4.3 mA. As for D_2/D_1 , a close correlation was noted for T_4/T_1 at low and high currents ($r = 0.95$, Figure 3). The mean bias between T_4/T_1 @TS+10 mA and T_4/T_1 @60 mA was -0.04 , and the 95% limits of agreement were -0.14 and $+0.06$ (Figure 4).

Discussion

Theoretically, stimulating current should not influence the fade ratio; the recruitment of motor nerve fibres by the stimulating current does not discriminate among motor units with different tendencies for fade. Nevertheless, before initiating this study, we were concerned that low-current testing might exert a marked effect on D_2 of DBS. The D_2 response would be spuriously low if, at 10 mA above the D_2 threshold, the second mini-tetanic burst failed to recruit enough fibres to overcome muscle elastic forces to the same relative degree as stimulation at 60 mA. Paired *t* testing indicated that the D_2/D_1 ratios at the lower current were less than their 60 mA counterparts. However, the mean difference of 0.02 indicates that the difference between ratios was of no clinical importance.

The present data supplement previous findings obtained with TOF and DBS at low currents.^{10,21-23, 27} It has been shown previously that DBS and TOF maintain a high degree of correlation at 20, 30 and 50 mA,²⁴ but no attempt had been made to perform inter-current comparisons among DBS readings or to standardize the stimulating current according to the D_2 threshold. By standardizing the stimulating current to 10 mA above threshold, excessively low currents may be avoided, and a "constant" stimulus can be provided despite changes in impedance that may occur during long surgical procedures. We elected to evaluate prospectively D_2/D_1 at a current of 10 mA above threshold, because our retrospective analysis of T_4/T_1 data had indicated that this was the lowest current which provided consistent determinations of fade.²² Whereas the discomfort associated with DBS at this current has not been established, it should be less than the VAS pain score of 5.5 reported by awake volunteers who received DBS at 30 mA (vs a VAS score of 7.0 at 50 mA).⁷

The limits of agreement obtained for T_4/T_1 in the present study are similar to the limits obtained in previous investigations.²⁸ However, the precision (i.e., the repeatability of the measurement under identical conditions) of low-current determinations is less than that of high-current determinations.^{22,27} These findings may be attributable, in part, to the limited resolution of our monitoring equipment. In the setting of intense block and/or upon stimulation with low current, evoked twitches may be of low amplitude, and precise measurement may be difficult. The greater amplitude of the DBS-evoked responses may account for the greater precision achieved with this technique than with TOF.

It should be noted that greater precision may not always be attained at higher currents. High currents may stimulate directly long flexors of the forearm or induce repetitive firing.²⁸ The need for thumb repositioning²⁹ and the likelihood of transducer overload³⁰ also may be

greater at high currents. In addition, the greater precision reported with high currents in anaesthetized patients^{22,27} may not be maintained in awake patients if pain affects their compliance. In this regard, retrospective assessment of data obtained in PACU patients who were recovering from general anaesthesia and pancuronium for muscle relaxation¹⁰ reveals that the intra-current difference (mean $\pm 2 \times$ SD) at 50 mA was -0.01 ± 0.08 ; the precision was only slightly better than that obtained at 20 mA ($+0.02 \pm 0.12$). In an ongoing assessment of electromyographic monitoring at varying currents, 4 of 19 unmedicated volunteers withdrew from the study because they were unable to tolerate train-of-four stimulation at supramaximal current. Moreover, irrespective of its potential benefits in awake patients, DBS at low current afforded more sensitive subjective (i.e., visual and tactile) assessment of fade than its high-current counterpart.¹ Hence, low-current testing may be preferable in settings where a mechanographic device is not employed.

We conclude that D_2/D_1 , as well as T_4/T_1 , assessments of fade may be performed at 10 mA above the D_2 or T_4 threshold with minimal bias and with a clinically acceptable increase in variability.

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