Recovery of train-of-four after mivacurium

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The present study was designed to determine the time-course of recovery of the train-of-four (TOF) ratio during spontaneous recovery from mivacurium-induced block. Fifteen patients, free of neuromuscular disease, undergoing general endotracheal anaesthesia with isoflurane were studied. After anaesthetic induction, patients received a bolus dose of mivacurium $0.15 \text{ mg} \cdot \text{kg}^{-1}$. The TOF was then recorded continuously every 12 sec with a mechanogram (adductor pollicis monitor). When the TOF ratio recovered spontaneously to 0.9, an additional $0.05 \text{ mg} \cdot \text{kg}^{-1}$ of mivacurium was given. The durations required for recovery from a TOF ratio of 0.3 to 0.7 ($\text{DUR}_{0.3-0.7}$) and from a TOF ratio of 0.3 to 0.9 ($\text{DUR}_{0.3-0.9}$) were determined. The $\text{DUR}_{0.3-0.7}$ averaged $7.0 \pm 2.5 \text{ min}$ (range 3.4–12.2 min). The $\text{DUR}_{0.3-0.9}$ averaged $11.8 \pm 3.9 \text{ min}$ (range 6.0–20.2 min). There was no evidence of prolongation of recovery times (cumulation) following repeated dosing. The present data indicate that, in patients with normal cholinesterase activity (clinical duration 7–25 min), waiting 20 min beyond the time when fade is no longer apparent by visual or tactile evaluation is sufficient to attain a TOF ratio greater than 0.7–0.9 during spontaneous recovery from mivacurium, and may enable anaesthetists to avoid antagonism of mivacurium-induced block.

La présente étude a pour objectif de déterminer le déroulement temporel au train de quatre (TOF) de la décurarisation spontanée du bloc neuromusculaire initié au mivacurium. Quinze patients, indemnes de toute maladie neuromusculaire, soumis à une anesthésie générale à l'isoflurane sont étudiés. Après l'in-

duction de l'anesthésie, ils reçoivent un bolus de mivacurium $0,15 \text{ mg} \cdot \text{kg}^{-1}$. Le TOF est enregistré en continu à toutes les 12 secondes avec une jauge de contrainte (moniteur de l'adducteur du pouce). Quand le TOF a récupéré spontanément à 0,9, une dose supplémentaire de mivacurium $0,05 \text{ mg} \cdot \text{kg}^{-1}$ est administrée. Les délais requis pour que le rapport du TOF passe de 0,3 à 0,7 ($\text{DUR}_{0.3-0.7}$) et de 0,3 à 0,9 ($\text{DUR}_{0.3-0.9}$) sont déterminés. En moyenne, le $\text{DUR}_{0.3-0.7}$ est de $7,0 \pm 2,5 \text{ min}$ (entre 3,4 et 12,2 min). Le $\text{DUR}_{0.3-0.9}$ moyen est de $11,8 \pm 3,9 \text{ min}$ (entre 6,0 et 20,2 min). On n'a pas mis en évidence de récupération retardée après des doses répétées (cumulation). Les données actuelles indiquent que chez les patients dont l'activité cholinestérasique est normale (durée 7 à 25 min), une attente de 20 min après la disparition visuelle ou tactile de l'affaiblissement de la réponse (fade) suffit pour obtenir un TOF plus élevé que 0,7 à 0,9 pendant la récupération spontanée au mivacurium, et permet à l'anesthésiste de s'abstenir de décurariser avec un antagoniste lorsque la curarisation est produite par du mivacurium.

Key words

MEASUREMENT TECHNIQUES: train-of-four;
NEUROMUSCULAR RELAXANTS: mivacurium;
RECOVERY: non-depolarizing relaxants; spontaneous.

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A potential advantage of short-acting neuromuscular blocking agents is that rapid spontaneous recovery of neuromuscular function may obviate the need for antagonism with anticholinesterases.¹⁻³ Although generally considered benign, reversal may be associated with nausea and vomiting, alterations in heart rate, weakness due to overdosing, and dry mouth as a result of antisialagogue coadministration. Alternatively, spontaneous recovery typically requires more time and necessitates an appreciation as to when the degree of recovery is adequate. Failure to appreciate adequate recovery would unnecessarily delay tracheal extubation; failure to identify residual block may lead to premature tracheal extubation, postoperative weakness, and inability to maintain and protect the airway.

In the absence of clinical signs to the contrary, a train-of-four (TOF) ratio >0.7 at the adductor pollicis muscle (defined as the ratio of the amplitude of the fourth evoked response to that of the first during TOF stimulation of the ulnar nerve)⁴ generally has been considered to be indicative of adequate recovery from nondepolarizing block. A greater margin of safety is obtained if tracheal extubation is delayed until the TOF ratio has reached 0.9. Unfortunately, unless mechanical recording devices such as the electromyogram or adductor pollicis force

transducer are used (which is not the usual clinical practice), anaesthetists may fail to identify TOF by visual inspection or tactile assessment even when the mechanographic TOF ratio confirms pronounced fade (e.g., a TOF ratio as low as 0.3–0.4).^{5–11} Thus, if spontaneous recovery without anticholinesterases antagonism is planned, it would be important to have an appreciation of the time required for the TOF ratio to increase from approximately 0.3 to 0.9 ($DUR_{0.3-0.9}$). The present investigation was undertaken to document this interval during spontaneous recovery from the short-acting relaxant mivacurium chloride (Mivacron, Burroughs Wellcome Co., Research Triangle Park, NC).

Methods

Following approval by the institutional Human Investigation Committee at Yale University School of Medicine, 15 consenting patients ranging in age from 17 to 78 yr were studied. Patients were within 50% of their ideal body weight, with an ASA physical status of 1, 2 or 3. They were free of known neuromuscular disease and were not receiving any medications known to affect neuromuscular function. Nerve stimulation consisted of four supramaximal 0.2 msec square-wave stimuli (at 2 Hz) delivered every 12 sec by an Innervator NS 252 stimulator (Fisher & Paykel, Auckland, New Zealand). Prior to the start of the clinical investigation, the nerve stimulator was bench tested (to confirm consistent current output) by interfacing it with a Tektronix 7623A oscilloscope (Tektronix, Inc., Beaverton, OR). For intraoperative neurostimulation, surface electrodes were placed along the ulnar nerve over the olecranon groove and on the volar aspect of the forearm. The ipsilateral thumb was inserted into an adductor pollicis force transducer (APM-L, Life-Tech, Inc., Houston, TX), which was interfaced with a monitor and strip chart recorder (Datascope 2000 A/RS, Datascope Corp, Paramus, NJ).

General anaesthesia was induced with thiopentone (4–6 mg · kg⁻¹), fentanyl (1–2 µg · kg⁻¹) and midazolam (0.02–0.04 mg · kg⁻¹) *iv*, and was maintained with isoflurane (0.75% to 1.0% end-tidal) with 66% nitrous oxide in oxygen. After induction of anaesthesia, a stable baseline response to TOF was recorded. Patients then received mivacurium, 0.15 mg · kg⁻¹ *iv*, and TOF monitoring was continued every 12 sec for the remainder of the surgical procedure.

The study period was initiated when the mechanographic TOF ratio recovered to 0.3. The times required to attain ratios of 0.7 and 0.9 were measured, and the $DUR_{0.3-0.7}$ and $DUR_{0.3-0.9}$ were determined. Upon completion of the first study period (i.e., after the TOF ratio reached 0.9), a second dose of mivacurium (0.05 mg · kg⁻¹) was administered *iv*, and recovery was again

FIGURE Times (mean $\pm$ SD) to attain a TOF ratio of 0.7 and 0.9 after a TOF ratio of 0.3 is documented with an adductor pollicis monitor during spontaneous recovery from mivacurium. There were no differences in the recovery times among the four sequential mivacurium doses.

allowed to occur spontaneously. The times of recovery to TOF ratios of 0.3, 0.7, and 0.9 again were measured. As many as four spontaneous recovery periods ($DUR_{0.3-0.9}$) were monitored in each patient. The mean, standard deviation (SD), and range for the $DUR_{0.3-0.7}$ and $DUR_{0.3-0.9}$ were calculated. The influence of a potential cumulative effect after repeated mivacurium injections was assessed by comparing the recovery intervals after each subsequent injection to that after the first injection using paired *t* test; for all analyses, $P < 0.05$ was considered statistically significant.

Results

Patients (eight male and seven female), ASA physical status 1–3, were 52 ± 20 yr old, weighed 75 ± 15 kg, and were 173 ± 9 cm in height.

There were a total of 49 recovery periods monitored in the 15 patients. The $DUR_{0.3-0.7}$ averaged 420 ± 147 sec (7.0 ± 2.5 min), with a range of 202–730 sec (3.4–12.2 min). There was no evidence of a cumulative effect with repeated doses; the $DUR_{0.3-0.7}$ after the first mivacurium dose averaged 421 ± 143 sec (7.0 ± 2.4 min), while that after the fourth dose averaged 438 ± 166 sec (7.3 ± 2.8 min) ($P = \text{NS}$; Figure). For each patient, the $DUR_{0.3-0.7}$ was similar among each of the four sequential drug administrations; $P = \text{NS}$ for differences among them.

The study interval which provided the greater margin

of safety in the clinical setting, the $DUR_{0.3-0.9}$, averaged 710 ± 233 sec (11.8 ± 3.9 min) with a range of 358–1,212 sec (6.0–20.2 min). Again, there were no statistically significant differences between study periods (i.e., no evidence of cumulation). The $DUR_{0.3-0.9}$ after the first mivacurium dose was 710 ± 241 sec (11.8 ± 4.0 min), while after the fourth administration it was 707 ± 283 sec (11.8 ± 4.7 min) (Figure).

The time from drug administration until recovery of twitch to 25% of baseline (clinical duration, or $T_{25\%}$) in the 15 patients was 678.3 ± 309 sec (11.3 ± 5.1 min), with a range of 400–1462 sec (6.7–24.4 min).

Discussion

Residual neuromuscular block has been documented in up to 44% of patients recovering from general anaesthesia with nondepolarizing neuromuscular relaxants,⁵⁻⁷ particularly after administration of long-acting drugs. Although the incidence should be lower after a short-acting agent such as mivacurium, residual block nevertheless remains a potential complication.

Most pharmacodynamic investigations focus on the times required for return of twitch height to 25% and 95% of baseline, and the time required for an increase from 25% to 75% of baseline twitch height. However, in the clinical setting we most commonly rely upon TOF monitoring for assessing the adequacy of recovery. As noted above, fade associated with a degree of block that causes a mechanographic TOF ratio as low as 0.3 (and occasionally even lower) may be unappreciated by visual or tactile assessment.⁵⁻¹¹ Thus, clinicians are faced with the question of how long to delay tracheal extubation once the four responses to TOF appear to be equal by subjective assessment. In the present study, once it returned to a value of 0.3 during spontaneous recovery from mivacurium-induced block, the TOF ratio reached 0.7 and 0.9 in 420 ± 147 sec (7.0 ± 2.5 min) and 710 ± 233 sec (11.8 ± 3.9 min), respectively. These data indicate that 97.5% of patients in the present population would reach a TOF ratio of 0.9 within 19.3 min (i.e., mean plus 2 SD) once a TOF ratio of 0.3 is achieved.

The present data also demonstrate the consistency of recovery following repeated doses of mivacurium, in agreement with the lack of accumulation reported in previous investigations.^{12,13} The wide inter-patient variability with respect to recovery time may be attributable, in part, to the varying degrees of plasma cholinesterase activity among patients. However, recovery times were consistent within a given patient, documenting the lack of cumulation in our study population.

Admittedly, the present findings do not provide a method for guaranteeing adequacy of recovery from mivacurium. A deficiency of enzyme activity – as may be

indicated by an exaggerated response to a given dose of mivacurium or by delayed return of a detectable twitch – would lead to prolongation of the final phases of recovery. However, this was not the case in our 15 patients: the mean clinical duration was 11.3 min, while the longest clinical duration was 24.4 min. Recovery also may be compromised by the myriad of factors which affect neuromuscular block, including anaesthetic agents, hypothermia, acidosis, hypercarbia, and antibiotic use. In addition, degrees of fade associated with a TOF ratio below 0.3 occasionally may be undetected by visual or tactile assessment. Moreover, a patient's ability to maintain and protect his or her airway is not guaranteed by either of the TOF endpoints utilized in the present study (i.e., TOF ratios of 0.7 or 0.9). Nevertheless, the present data do provide a framework for gauging when recovery of the TOF ratio is likely to be "adequate," and for planning tracheal extubation and the tests of ventilatory function that should precede it.

In conclusion, we have provided a framework for assessing when spontaneous neuromuscular recovery from mivacurium may be adequate to allow extubation of the trachea. As is the case even when a reversal agent is administered, each patient must be evaluated on an individual basis, and this may be especially critical if spontaneous recovery is allowed to occur: spontaneous recovery may provide a smaller margin of safety than anticholinesterase-aided reversal, and is highly dependent on plasma cholinesterase activity. If the dose-response and/or duration of action have been beyond the typical clinical range, then subsequent recovery may be unduly prolonged.

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