Tetanus-induced Changes in Apparent Recovery after
Bolus Doses of Atracurium or Vecuronium

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The current study evaluated the duration and magnitude of posttetanic effects in 56 patients recovering from a bolus dose of nondepolarizing relaxant to assess the impact of tetanus on monitoring in a common clinical setting. After induction of general anesthesia (thiopental, fentanyl, oxygen, nitrous oxide, and isoflurane), a baseline response to train-of-four (TOF) stimulation was recorded using an adductor pollicis force transducer, and the ratio of the fourth response (T₄) to the first (T₁) was calculated. Patients then received a bolus dose of either atracurium 0.50 mg·kg⁻¹ (n = 28) or vecuronium 0.10 mg·kg⁻¹ (n = 28). TOF was recorded at 12-s intervals between 25% and 75% recovery of T₁ (time₃₅-₇₅, first data set); then, block was reestablished with the same agent (atracurium 0.10 or vecuronium 0.02 mg·kg⁻¹), and monitoring of time₃₅-₇₅ was repeated (second data set). Subjects were randomized such that none, one, or both sets had TOF monitoring interrupted by a 5-s, 50-Hz tetanic stimulus at 50% recovery (TET). For each drug, 7 patients were assigned to each of the four possible sequences: no tetanus (NOTET) set followed by NOTET-TET; TET-NOTET; and TET-TET. After either drug, the TET data sets demonstrated significant acceleration of recovery of T₁ from 50% to 75% (time₃₅-₇₅) of its baseline height (P < 0.05 by paired t test). After atracurium, time₃₅-₇₅ was shortened by the tetanic stimulation from a control of 6.3 ± 1.4 to 5.0 ± 1.3 min (P < 0.05). After vecuronium, time₃₅-₇₅ was shortened from 7.4 ± 2.8 to 5.0 ± 2.6 min (P < 0.05). We conclude that, when delivered at 50% recovery of single twitch height, tetanus shortens the time to 75% recovery after atracurium or vecuronium, such that the response of the tested site may no longer be representative of other muscle groups. (Key words: Monitoring, neuromuscular; fade; nerve stimulator; posttetanic facilitation; tetanic stimulation; time to recovery; train-of-four. Neuromuscular relaxants: atracurium; vecuronium.)

We recently reported that, after tetanic stimulation for 5 s at 50 Hz, the “facilitated” (or “potentiated”) heights of the first and fourth responses (T₁ and T₄) to train-of-four (TOF) stimulation returned to within 10% of their pretetanic baselines in 34 and 43 s, respectively. The effects of tetanus on the response to a subsequent tetanus likewise were short-lived: no effect was noted upon testing at 5-min intervals. These data were obtained during a continuous vecuronium infusion, which had been selected because it provided stable study conditions.

In the clinical setting, however, most anesthesiologists use bolus doses of relaxant. After an initial rapid increase in plasma concentration of relaxant, bolus administration is characterized by a gradual decrease in plasma concentration. The resultant concentration gradient between the neuromuscular junction and plasma may alter the response to a tetanic stimulus. This setting therefore may be different from that in which previous assessments had been made. The current randomized, controlled study was undertaken to document the effect of a 5-s, 50-Hz tetanic stimulus in this context, i.e., during recovery from bolus doses of atracurium or vecuronium. These intermediate-duration nondepolarizing agents were chosen because their relatively short half-life provides a dynamic, commonly encountered clinical setting.

Materials and Methods

After institutional review board approval, 56 consenting ASA physical status 1–3 patients undergoing elective general endotracheal anesthesia were studied. All patients were free of neuromuscular, renal, or hepatic disease; were within 25% of ideal body weight; and were not taking any medications known to interfere with neuromuscular function.

After induction of general anesthesia with intravenous thiopental (4–6 mg·kg⁻¹) and fentanyl (1–2 µg·kg⁻¹), anesthesia was maintained with 0.5–1.5% end-tidal isoflurane and 66% nitrous oxide in oxygen delivered by face mask. Succinylcholine 0.5–1.0 mg·kg⁻¹ was administered for facilitation of endotracheal intubation. After return of neuromuscular function, stimulation of the ulnar nerve was accomplished with a DualStim Plus (Professional Instruments, Houston, TX) via surface electrodes (Cleartrace ECG Electrodes, Medtronic, Inc., Haverhill, MA) placed on the volar forearm with the negative electrode distal to the positive electrode. The nerve stimulator was adjusted to deliver 200-µs, square-wave impulses at 70 mA (the stimulator’s maximal current output). Neuromuscular responses were monitored with an adductor pollicis force transducer (Myotrace APM-1, Professional Instruments, Houston, TX) and were recorded on an interfaced strip-chart recorder (Datascope 2000 A/RS, Datascope Corp., Paramus, NJ). The thumb was abducted to a preload of 250–300 g, and responses to TOF stimulation were recorded at 12-s intervals (0.083 Hz). The amplitude of thumb adduction was estimated to the nearest 0.5 mm by freezing the TOF tracing on the monitor screen and adjusting the built-in monitor reference line in 1-mm increments. The T₁ and T₄ heights and the

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T₄/T₁ ratio obtained in the absence of nondepolarizing block were recorded; these served as baseline values for subsequent comparisons. Patients then were assigned randomly to receive either atracurium (0.50 mg · kg⁻¹, n = 28) or vecuronium (0.10 mg · kg⁻¹, n = 28) for induction of muscle relaxation.

TOF stimulation at 0.083 Hz was continued during recovery of neuromuscular block, and the amplitude of T₁ was recorded continuously and expressed as a percent of its baseline height. When T₁ recovered to 25% and then to 50% of its baseline height, the values for T₁, T₄, and T₄/T₁ were recorded. Once 50% recovery of T₁ had been achieved, each patient was randomly assigned to one of four stimulating sequences designed to evaluate the effects of tetanus on subsequent recovery. Each sequence consisted of two consecutive testing periods (“sets”) during which TOF monitoring at 0.083 Hz was continued, and the times for 25–50% and 50–75% recovery of T₁ were measured (fig. 1). Sequence 1 (NOTET-NOTET) consisted of TOF monitoring until 75% recovery of T₁ (first set), followed by administration of a supplemental dose of the same relaxant (atracurium 0.10 mg · kg⁻¹ or vecuronium 0.02 mg · kg⁻¹) and continuation of TOF monitoring until 75% recovery was again achieved (second set). In sequence 2 (TET-NOTET), a tetanic stimulus (50-Hz, 5-s) was delivered in the second set upon recovery of T₁ amplitude to 50%; 4 s after tetanus, TOF stimulation was resumed until 75% recovery of T₁. In sequence 3 (TET-NOTET), tetanus was delivered in the first set upon T₁ recovery to 50%, and the second 25–75% recovery period proceeded without an intervening tetanus. In sequence 4 (TET-TET), tetanus was delivered after both the first and second recoveries of T₁ amplitude to 50% (i.e., in both first and second sets) (fig. 1).

For each patient, the times to 25% recovery of T₁ (timeₑ₂₅%), 50% recovery of T₁ (timeₑ₅₀%), and 75% recovery of T₁ (timeₑ₇₅%) were recorded, and the intervals between them (timeₑ₅₀₋₇₅% and timeₑ₂₅₋₅₀%) were measured. The degree of posttetanic facilitation was calculated as the posttetanic increase in the height of T₁ divided by the pretetanic height, multiplied by 100. Group data were expressed as mean ± standard deviation. The times for recovery within each of the four sequences were compared using paired t test. Overall effects of tetanus on recovery were analyzed with unpaired t test. A value of P < 0.05 was considered to be statistically significant for all analyses.

**Results**

The 56 patients had a mean (± standard deviation) age of 51.2 ± 18 yr (range 20–79 yr), height of 171.4 ± 10 cm (range 152–188 cm), and weight of 73.9 ± 13 kg (range 50–105 kg) (P = no significant difference [NS] for comparisons between atracurium and vecuronium groups or between TET and NOTET data sets). As summarized in table 1, the data clearly indicate an effect of tetanus on the ensuing rate of T₁ recovery (i.e., on timeₑ₅₀₋₇₅%). Overall, the timeₑ₅₀₋₇₅% was shortened from 6.3 ± 1.1 to 5.0 ± 1.3 min in patients who received atracurium (P < 0.05) and from 7.4 ± 2.8 to 5.0 ± 2.6 min in patients who received vecuronium (P < 0.05).

In patients receiving atracurium in which only one of the two sets included tetanic stimulation (sequences 2 and 3), timeₑ₅₀₋₇₅% after tetanus was significantly shorter than that noted for the corresponding NOTET set (P < 0.05). This was in contrast to the similar timeₑ₅₀₋₇₅% noted in the sequence during which neither set received tetanus (sequence 1, P = NS) or in which both sets received tetanus (sequence 4, P = NS). The influence of tetanus on subsequent recovery after atracurium also was seen in that timeₑ₅₀₋₇₅% was significantly shorter than timeₑ₂₅₋₅₀% in the TET data sets (P < 0.05 in the second set of sequence 2, in the first set of sequence 3, and in both sets of sequence 4). In contrast, these times were similar (P = NS) in NOTET sets. The effect of tetanus on the rate of recovery between timeₑ₂₅% and timeₑ₇₅% is illustrated in figure 2. It was most prominent during the 60–70 s after its delivery, as T₁ returned to its lowest value 64 ± 14 s after the tetanic stimulation. However, T₁ did not return to its pretetanic baseline of 50% recovery: its lowest posttetanic value was equivalent to 61% recovery. Spontaneous recovery in the NOTET sets at this time amounted to only 56%.

![Fig. 1. Study protocol employed independently for patients receiving atracurium (n = 28 pairs) or vecuronium (n = 28 pairs). TET = tetanus delivered at 50% recovery of first twitch; TOF = train-of-four.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931325/ on 06/22/2017)
Table 1. Recovery Times (min)

<table>
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<tr>
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<th>First Set</th>
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<th>Second Set</th>
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<tr>
<td></td>
<td>Time 25-50</td>
<td>Time 50-75</td>
<td>Time 50-75</td>
<td>Time 50-75</td>
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<td>I, NOTET-NOTET</td>
<td>5.7 ± 1.1</td>
<td>5.7 ± 1.1</td>
<td>6.2 ± 0.7</td>
<td>6.3 ± 1.1</td>
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<tr>
<td>II, NOTET-TET</td>
<td>6.6 ± 1.4</td>
<td>6.6 ± 1.1</td>
<td>6.3 ± 0.9</td>
<td>4.4 ± 0.5*†</td>
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<tr>
<td>III, TET-NOTET</td>
<td>6.2 ± 1.1</td>
<td>4.9 ± 1.1*†</td>
<td>6.2 ± 1.3</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>IV, TET-TET</td>
<td>6.6 ± 1.4</td>
<td>4.7 ± 1.2†</td>
<td>7.6 ± 1.3</td>
<td>6.0 ± 1.7†</td>
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<tr>
<td>Vecuronium</td>
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<tr>
<td>I, NOTET-NOTET</td>
<td>6.2 ± 1.4</td>
<td>6.2 ± 1.0</td>
<td>7.8 ± 2.3</td>
<td>8.4 ± 8.3</td>
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<tr>
<td>II, NOTET-TET</td>
<td>5.8 ± 3.2</td>
<td>6.5 ± 3.4</td>
<td>6.9 ± 3.4</td>
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<td>III, TET-NOTET</td>
<td>6.5 ± 1.9</td>
<td>4.7 ± 1.8*†</td>
<td>8.4 ± 3.6</td>
<td>8.4 ± 3.0</td>
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<tr>
<td>IV, TET-TET</td>
<td>5.3 ± 1.7</td>
<td>4.5 ± 2.3†</td>
<td>6.5 ± 2.1</td>
<td>5.5 ± 2.9†</td>
</tr>
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NOTET = no tetanus delivered at 50% recovery of single twitch; TET = tetanus delivered at 50% recovery of single twitch.

* P < 0.05 for Time 50-75 in NOTET and TET sets of a given sequence.
† P < 0.05 for Time 25-50 vs Time 50-75 in TET sets.

The statistical separation after vecuronium was less clear because there was greater variability with respect to recovery times even in the absence of an intervening tetanus. However, similar to the groups of patients receiving atracurium, all vecuronium TET data showed acceleration of time 50-75, whereas none of the NOTET data showed this acceleration. As illustrated in figure 3, T1 returned to its lowest value 65 ± 15 s after tetanic stimulation. Again, T1 did not return to its pretetanic baseline: its lowest posttetanic value was equivalent to 61% recovery. At the corresponding time, spontaneous recovery in NOTET sets amounted to only 52%.

Tetanus (delivered at 50% recovery) had no apparent effect on the degree of fade evident at 75% recovery of T1. In the atracurium sets, the T4/T1 ratios at time 50% were 0.29 ± 0.1 and 0.27 ± 0.1 in the NOTET and TET sets, respectively. The respective T4/T1 ratios achieved by 75% recovery of T1 were 0.46 ± 0.1 and 0.40 ± 0.1, respectively (P = NS). In the vecuronium sets, the T4/T1 ratios at time 50% were 0.25 ± 0.1 and 0.22 ± 0.1 in the NOTET and TET sets, respectively. The corresponding T4/T1 ratios at 75% recovery of T1 were 0.42 ± 0.1 and 0.39 ± 0.2 (P = NS).

Discussion

The current data indicate that a 5-s, 50-Hz tetanic stimulus shortens the time 50-75% recovery after a bolus dose of atracurium or vecuronium. This recovery time was shortened even though T1 and T4 were found typically to return to their lowest posttetanic heights within 2 min after tetanic stimulation. The overall effect on T1 was paralleled by that on T4; T4/T1 ratios at 75% recovery of T1 were equivalent in the TET and NOTET sets.
On initial inspection, the "acute" effects of tetanus on TOF monitoring in the current study appeared to be similar to those noted previously during a continuous infusion of relaxant. The percent potentiation of $T_1$ amplitude and the time until return to its lowest posttetanic value were similar in both studies. However, certain differences may be identified. In the study performed during continuous infusion, we stated that $T_1$, $T_4$, and $T_4/T_1$ returned to baseline within 74 s. In that setting, return to baseline was defined as the return of $T_1$ to within 10% of pretetanic amplitude. Retrospective analysis of those data noted that $T_1$ actually had returned to an amplitude that was 2.75 ± 4% below its pretetanic height. In contrast, in the current study, $T_1$ returned to an amplitude (61%) that was 22% above its pretetanic height (50%) after both atracurium and vecuronium. The interval between the time of 50% recovery of $T_1$ and the return of $T_1$ to its lowest posttetanic value amounted to a rate of recovery that was 100–200% greater than the recovery rate in data sets in which tetanus was not delivered. Subsequent rates of recovery were nearly equal and were similar to those noted for time$_{25-50\%}$.

The major difference between the steady state attained with a continuous infusion of relaxant and the dynamic state during recovery after a bolus injection is the tissue-to-plasma gradient that characterizes the latter state. Subsequent gradients may exist among the receptors, the junctional fluid, and other parts of the biophase. If a gradient were responsible for the prolonged posttetanic effects noted in the current study, then it is tempting to reconsider "displacement" as a mechanism for the posttetanic effects. The relaxant displaced by tetanus-induced acetylcholine release may follow the gradient(s) established during recovery and thereby leave the neuromuscular junction. Such displacement may occur pre- and/or postsynaptically. However, a more simple explanation is that the increase in tissue perfusion induced by tetanus accelerates the removal of drug away from the junction along its concentration gradient.

We chose to evaluate the interval between 25% and 75% recovery of $T_1$ because recovery tends to be linear and relatively independent of the dose of relaxant in this range; in contrast, recovery between 0 and 25% and between 75% and 100% tends to be nonlinear. Although this study was not designed to compare atracurium to vecuronium, certain differences were noted. Before 50% recovery and assignment to one of the four stimulating sequences, recovery (i.e., time$_{25-50\%}$) from vecuronium tended to be more variable. This difference persisted in NOTET data sets throughout the study period, consistent with a previous report of wide scatter in the various estimates of elimination half-life. Evaluation of the effects of tetanus at 50% recovery of $T_1$ permitted documentation of a preintervention period in all data sets as well as a period of posttetanic effects. Indeed, in patients receiving vecuronium, time$_{25-50\%}$ was longer during the second recovery period. Admittedly, isoflurane may affect neuromuscular function. Although requirements for isoflurane differed among patients, the isoflurane concentration varied by less than 0.25% within each study period. It is therefore unlikely that isoflurane contributed significantly to differences within groups.

In conclusion, tetanus delivered at 50% recovery of $T_1$ accelerates recovery during the period of posttetanic potentiation. The effects of this transient acceleration of recovery persist at least until 75% recovery of $T_1$. This "long-term" effect of tetanus after a bolus dose of an intermediate-acting relaxant is in contrast to the brief effect previously noted during the steady state that characterizes a continuous infusion. Although the changes induced by tetanus were relatively small, they nevertheless suggest that subsequent neuromuscular testing at the same site may be altered. Monitoring at the adductor pollicis muscle after tetanic stimulation may lead one to overestimate the extent of recovery at that site. This may lead to unnecessary repeated administration of neuromuscular blocking agents, or at the other extreme, to false estimation that adequate neuromuscular function exists.

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References