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Antagonism of Mivacurium-induced Neuromuscular Blockade in Humans

Edrophonium Dose Requirements at Threshold Train-of-Four Count of 4

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Background: **Mivacurium's rapid rate of recovery has led to the suggestion that routine reversal of its residual effects may be unnecessary once signs of spontaneous recovery are evident. When antagonism is attempted at 90% twitch depression, the time saved to return to train-of-four (TOF) ratios >0.70 compared to control has been reported to average ≤8 min. This study was an attempt to determine whether similar savings in time could be achieved once spontaneous recovery was well underway. Also investigated was the ability of a TOF count of 4 to serve as a marker that might predict the dose of edrophonium necessary for satisfactory antagonism of mivacurium.**

Methods: **Fifty-eight adult patients were studied under nitrous oxide/propofol/opioid anesthesia. Neuromuscular block was monitored electromyographically and maintained by infusion of mivacurium at a level sufficient to abolish any palpable response of the thumb. TOF stimuli were delivered to the ulnar nerve at the wrist every 20 s throughout the period of observation. When the infusion was terminated, an observer was asked to note the time when the 1st through the 4th twitches first became detectable. In group 1, recovery to a TOF ratio >0.90 was allowed to proceed spontaneously. In groups 2, 3, and 4, 0.3, 0.5, and 0.75 mg/kg edrophonium, respectively, was administered when the 4th response to TOF stimulation first became palpable. Times to TOF ratios of 0.70 and 0.90 were recorded in all groups.**

Results: **TOF counts of 1, 2, 3, and 4 first became palpable at 8 ± 4% (SD), 20 ± 6%, 33 ± 9%, and 44 ± 10% of control twitch height. Fade on TOF stimulation could no longer be detected once the TOF ratio exceeded a value of 0.41 ± 0.07 (range 0.25–0.51). Once the 1st evoked response was palpable, the 2nd, 3rd, and 4th responses could be detected 2.5 ± 1.1 (SD), 4.6 ± 1.6, and 6.1 ± 1.6 min later. Spontaneous recovery to TOF fade ratios of 0.7 and 0.9 occurred on average 10.7 ± 2.3 and 16.9 ± 4.7 min, respectively, after a threshold count of 4. Administration of 0.3 mg/kg edrophonium shortened the recovery process by about 7.5 min. Increasing the dose of edrophonium beyond 0.3 mg/kg did not further accelerate recovery.**

Conclusions: **After recovery from profound mivacurium-induced neuromuscular block, TOF counts of 1, 2, 3, and 4 approximate 10%, 20%, 30%, and 40% return to control twitch height, respectively. Finally, ≥0.3 mg/kg edrophonium will accelerate recovery from mivacurium by approximately 7–8 min. (Key words: Antagonists, anticholinesterase: edrophonium. Monitoring: electromyography. Neuromuscular relaxants: mivacurium.)**

MIVACURIUM is the first clinically available nondepolarizing relaxant that can be categorized as an agent of short duration. After a dose of 2–3 times the ED_{95}, return to a train-of-four (TOF) ratio >0.7 has been reported to occur in approximately 30 min. In fact, once twitch height has returned to 25% of control (T1/Tc = 0.25), a TOF value >0.7 usually is present within 11–12 min.[1] This rapid rate of recovery has led to the suggestion that routine reversal of mivacurium's residual effects may be unnecessary once signs of spontaneous recovery are in evidence. This argument is not unreasonable because only a modest reduction in recovery time follows subsequent anticholinesterase administration. When antagonism is attempted with either edrophonium or neostigmine at T1/Tc ratios of 0.10, the time saved to return to TOF ratios >0.70 compared to control has been reported to average only about 8 min.[2]

This issue is not settled, however. In day-to-day clinical practice, a reduction in anesthesia time of 10 min,

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if obtainable, is often a worthwhile goal. In a busy ambulatory facility, a saving of 10 min per case multiplied by four or five cases per day may be meaningful in terms of improved institutional efficiency. In addition, no studies have attempted to correlate subjective estimates of recovery, such as the TOF count (TOFC) or the absence of TOF fade, with actual (quantitative) recovery intervals recorded after mivacurium administration. Finally, few studies have looked at the times to recovery of more rigorous endpoints, such as a TOF ratio >0.90 after mivacurium-induced neuromuscular block. In view of the wide interpatient variability with respect to recovery times[3] and reports that return of neuromuscular function also may be delayed after infusions of long duration,[4] additional studies of the clinical utility of mivacurium antagonism seemed warranted.

Methods and Materials

Fifty eight ASA physical status 1–2 adult patients (aged 18 to 65 yr) undergoing elective surgical procedures for which the administration of a muscle relaxant was appropriate were included in the study. All patients were free from neuromuscular disease and were within 15% of ideal body weight. The protocol was approved by our hospital's Human Subject Review Committee, and informed consent was obtained. Anesthesia was induced with 2.0–2.5 mg/kg intravenous propofol and maintained with inhalation of nitrous oxide (65–70% inspired), 60–90 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol, plus intravenous fentanyl supplementation as needed. Ventilation was controlled, and end-tidal carbon dioxide tension was maintained between 32 and 38 mmHg.

The indirectly evoked integrated compound action potential of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve at the wrist was measured and recorded using a Datex NMT221 System monitor. Supramaximal nerve stimulation was achieved using the nerve stimulator incorporated into the Datex unit (pulse width 100 ms, constant current, 0–70 mA range). The test hand was immobilized, and approximately 200–300 g of resting tension was applied to the thumb with a Velcro strap. Anesthesia was induced, and before any muscle relaxants were administered, Tc and TOF fade ratio (T4/T1) were established after a 5-min period of baseline stabilization. TOF stimulation was given every 20 s during the observation period. Single twitch depression (measured by the height of T1/Tc) and TOF fade were continuously recorded.

Mivacurium (0.20 mg/kg) was administered as a slow intravenous bolus over approximately 90 s. When twitch depression was maximal, the patient's trachea was intubated. An infusion of mivacurium (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was begun as soon as evidence of neuromuscular recovery was present and then adjusted to provide a level of twitch depression at which no detectable visual or palpable response to TOF stimulation was obtained but at which some minimal electromyographic response was present. In practice, this usually resulted in the maintenance of the twitch (T1) response at less than 6% of control. The duration of all infusions exceeded 75 min. When the need for surgical relaxation was over, the infusion was discontinued and spontaneous recovery was allowed to proceed.

Group 1 (Spontaneous Recovery, n = 16)

An observer (one of the authors) was asked to manually abduct the monitored thumb slightly and to report when the 1st through the 4th evoked responses first became palpable. The time at which no fade on TOF stimulation could be detected was measured, and the T4/T1 value at that point was recorded. The observer was unaware of the actual T1/Tc or T4/T1 ratios during this period. The times from the initial palpable response (threshold TOFC of 1, TOFC-1) until the TOF ratio reached values of 0.70 and 0.90 were noted. Once the TOF fade ratio exceeded a value of 0.90, if T1 amplitude had not returned to its initial value, the final T1 value achieved was accepted as control and all other T1 values measured during recovery were normalized according to this standard. Nitrous oxide was not discontinued until all measurements were recorded.

Group 2 (n = 15)

Protocol was identical to that in group 1 except that 0.006 mg/kg atropine was administered at a TOFC of 2, and 0.30 mg intravenous edrophonium was given rapidly as soon as the 4th evoked response was palpable. Subjective observations were concluded at that point.

Groups 3 (n = 15) and 4 (n = 12)

Protocol was identical to that in group 2 except that reversal was initiated with 0.5 or 0.75 mg/kg edrophonium, respectively, at TOFC of 4 (TOFC-4).

All data from each group were compared with like data from other groups using single factor-factorial

Table 1. Twitch Height *Versus* Control (T1/Tc) at Various Threshold Train-of-four Counts (TOFC) during Recovery from Mivacurium (n = 58)

	T1/Tc at TOFC = 1	T1/Tc at TOFC = 2	T1/Tc at TOFC = 3	T1/Tc at TOFC = 4
Mean	0.08	0.20	0.33	0.44
SD	0.04	0.06	0.09	0.10
Range	0.01–0.19	0.06–0.41	0.13–0.57	0.20–0.70

analysis of variance and Scheffé's F test for multiple comparisons. Observed differences were considered significant when $P < 0.05$.

Results

There were no statistically significant differences as to age, sex, weight, duration of infusion, or mivacurium requirements between groups. The average durations of infusion (±SD) in groups 1 through 4 were 144 ± 44, 128 ± 43, 128 ± 56, and 121 ± 43 min, respectively.

Single Twitch Recovery and Train-of-Four Count

After cessation of the mivacurium infusion, TOFCs of 1, 2, 3, and 4 first became palpable at T1/Tc values (±SD) of 0.08 ± 0.04, 0.20 ± 0.06, 0.33 ± 0.09, and 0.44 ± 0.10, respectively (table 1). Fade on TOF stimulation no longer could be detected once the T4/T1 ratio exceeded a value of 0.41 ± 0.07 (range 0.25–0.51). There were no significant differences in the amplitude of T1 at TOFC-4 in any of the four groups.

Group 1 (Spontaneous Recovery)

Once the 1st evoked response to ulnar nerve stimulation was palpable, the 2nd, 3rd, and 4th responses (±SD) could be detected 2.9 ± 0.9, 5.2 ± 1.1, and 6.7 ± 2.5 min later, respectively. These values were not different from figures obtained by pooling data from all 58 patients (table 2). Fade on TOF stimulation was no longer detectable 5.1 ± 2.54 min after TOFC-4. Recovery to TOF fade ratios of 0.7 and 0.9 occurred on average 10.7 ± 2.3 and 16.9 ± 4.7 min, respectively, after a threshold TOFC-4.

Table 2. Recovery Times after Cessation of Mivacurium Infusion

	TOFC-1 to TOFC-2	TOFC-1 to TOFC-3	TOFC-1 to TOFC-4
All groups (n = 58)	2.54	4.64	6.12
SD	1.06	1.56	1.6
Range	1.0–6.7	1.7–9.7	3.3–10.7

Values are given in minutes.

TOFC = train-of-four count.

Table 3. Recovery Times after Cessation of Mivacurium Infusion

	TOFC-1 to TOF = 0.7	TOFC-1 to TOF = 0.9
Spontaneous recovery (Group 1, n = 16)	17.38	23.60
SD	3.52	5.84
Range	12.7–24.0	17.3–40.0
Edrophonium 0.3 mg/kg (Group 2, n = 15)	10.11	15.67
SD	3.81	5.73
Range	6.7–21.3	10.3–30.0
Edrophonium 0.5 mg/kg (Group 3, n = 15)	8.51	14.07
SD	2.69	4.76
Range	5.3–14.7	7.7–24.3
Edrophonium 0.75 mg/kg (Group 4, n = 12)	9.25	15.41
SD	2.80	5.00
Range	5.7–15.0	8.3–24.0

Values are given in minutes. Antagonist was administered at TOFC-4 (Groups 2–4).

TOFC-1 = threshold train-of-four count of 1; TOF = train-of-four fade ratio.

Groups 2–4 (Edrophonium Reversal)

Edrophonium administration accelerated recovery from a TOFC-4 to TOF ratios of 0.70 and 0.90 by approximately 7–8 min ($P < 0.001$). Increasing dosage from 0.3 to 0.75 mg/kg did not result in any increase in the average amount of time "saved" compared to spontaneous recovery (tables 3 and 4). The interval from edrophonium administration to a TOF ratio ≥0.7 was 4.0 ± 2.8, 3.0 ± 1.8, and 3.1 ± 1.3 min in groups 2, 3, and 4, respectively. These differences were not

Table 4. Time "Saved" (min) *Versus* Spontaneous Recovery

Dose of Edrophonium (mg/kg)	TOFC-4 to TOF > 0.7	TOFC-4 to TOF > 0.9
0.30	6.7	7.3
0.50	7.8	8.4
0.75	7.6	7.7

TOFC-4 = train-of-four count of 4; TOF = train-of-four fade ratio.

statistically different from each other (figs. 1 and 2). The time intervals from edrophonium administration to return of the TOF ratio to a value ≥0.9 in groups 2, 3, and 4 were 9.5 ± 4.7, 8.5 ± 3.9, and 9.3 ± 3.7 min, respectively.

Discussion

Single Twitch Recovery and Train-of-Four Count

Almost 20 yr ago, Lee suggested that the number of indirectly evoked responses to TOF stimulation at the ulnar nerve might be used to quantitate the depth of neuromuscular block.[5] He noted that, after the administration of d-tubocurarine over the range of 75–100% block, the 4th, 3rd, 2nd, and 1st twitches became undetectable in that order. He reported that these responses then returned in a predictable manner: two twitches appearing at 10%, three at 20%, and four at 25% of Tc. These figures are widely cited in standard texts and review articles,[6–8] although no indication of the variability of this observation was reported. Our data (table 1) differ considerably from Lee's values.

In Lee's initial study of TOFC, he measured the mechanical response of the adductor pollicis in 34 individuals while looking for visible movement in the other fingers of the hand. Different muscles, however, differ in their sensitivity to muscle relaxants. At a time when T1 has returned to 25% of control at the adductor pollicis, T1 is likely to have recovered to 40% of control at the hypothenar muscles of the hand.[9]

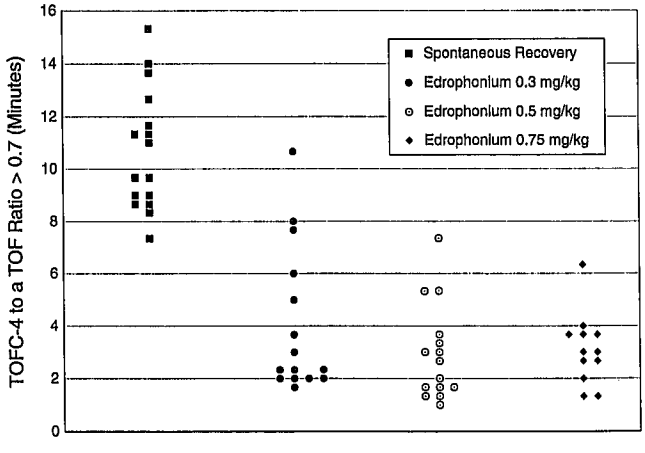

Fig. 1. Elapsed time from a threshold train-of-four count of 4 (TOFC-4) until the train-of-four (TOF) ratio reached a value of 0.7 or greater. Spontaneous recovery *versus* 0.3, 0.5, or 0.75 mg/kg edrophonium at TOFC-4.

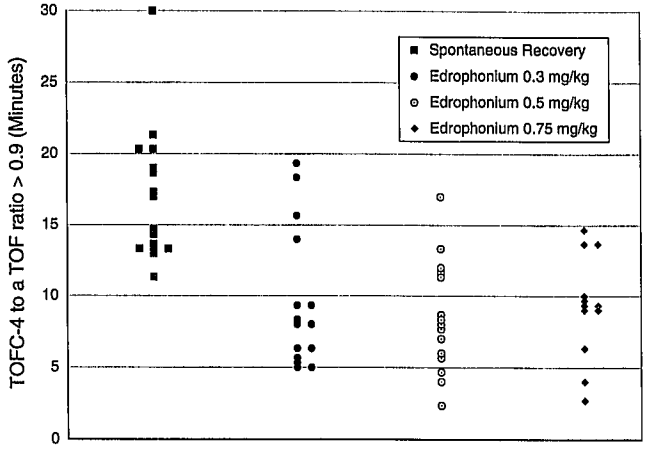

Fig. 2. Elapsed time from a threshold train-of-four count of 4 (TOFC-4) until the train-of-four (TOF) ratio reached a value of 0.9 or greater. Spontaneous recovery *versus* 0.3, 0.5, or 0.75 mg/kg edrophonium at TOFC-4.

In addition, TOFCs as determined by mechanomyographic recordings may have little relevance to what an observer can feel. Assuming a 40-mm full-scale pen deflection at T1 of 100%, evoked responses of <2% (0.5 mm) are recognized easily using chart recorders. Most observers, however, cannot palpate a 4th response to TOF stimulation until the height of the 4th twitch exceeds 5–6% of control (table 2). O'Hara *et al.*, for example, found that a TOFC-4 corresponded to only 15% of T1 recovery when this parameter was calculated from the mechanomyographic response displayed on a chart recorder.[10] In contrast, when the same investigators defined an evoked response as a visually observed movement of the hand, they found that a TOFC-4 represented 30–40% T1 recovery.[11] Another problem with mechanomyographic studies is that simultaneous quantitative and tactile responses of the same muscle group cannot be performed because accurate mechanical recordings of twitch tension require a constant preload. Electromyographic recordings of the adductor pollicis, however, compare well with mechanomyographic readings,[12] are less sensitive to preload, and hence enable subjective and objective responses to be obtained simultaneously from a single muscle group.

In view of the obvious importance of the TOFC as a tool for monitoring intraoperative neuromuscular function, it is surprising that few attempts have been made to validate Lee's observations, which were reported almost 20 yr ago. Except for the paper by O'Hara *et al.* noted above[11] and the data herein presented, we are unaware of other studies that have tried to correlate

subjective estimates of the TOFC with quantitative measurements of T1 recovery. Our observations strongly suggest that the commonly held impression that threshold TOFC-4 (as measured by thumb palpation) is synonymous with 25% return of T1 simply is not applicable during spontaneous recovery from mivacurium-induced neuromuscular block.

In summary, under the latter conditions, mean T1 twitch height at threshold TOFC-4 averaged 44% of control. As a rule of thumb, threshold TOFCs of 1, 2, 3, and 4 approximate return of T1 to 10%, 20%, 30%, and 40% of control, respectively. However, it should be recognized that, within these guidelines, considerable individual variability exists.

Group 1 (Spontaneous Recovery)

It is somewhat difficult to compare our recovery intervals with those of other authors, because we measured recovery times to TOF values of 0.70 and 0.90 from a subjective endpoint (TOFC) rather than a fixed T1/Tc value. Nevertheless, we believe our results are compatible with other published data. Brull reported average recovery times from a TOF ratio of 0.40 to 0.70 and 0.90 of 5.2 and 9.2 min, respectively.[3] These values are similar to the times we recorded from the point when fade was no longer palpable (TOF ratio = 0.41) to TOF ratios of 0.70 and 0.90 (5.5 and 11.8 min, respectively). Likewise, Savarese *et al.*[1] reported an average time for recovery from T1 of 5% of control to a TOF value of 0.70 after a mivacurium infusion of 17.8 min. This is essentially identical to our value (17.4 min) for TOFC-1 to TOF of 0.70 interval.

Our results also provide confirmation of Viby-Mogensen's *et al.* observation[13] that subjective evaluation of the presence or absence of TOF fade is unreliable. In none of the 16 patients in group 1 was fade detected once the TOF ratio exceeded 0.51. Of greater concern, fade was missed in two individuals who had TOF ratios <0.30.

Groups 2–4 (Edrophonium Reversal)

We chose to attempt reversal at a TOFC-4 rather than at deeper levels of neuromuscular block for several reasons. First, we believe that, because the TOFC-1–3 and TOFC-2–4 intervals are so short (4.6 ± 1.6 min, range 1.7–9.7, and 3.6 ± 1.2 min, range 1.7–8.3, respectively), the time "wasted" in recording these intervals is time well spent. General recommendations regarding the need for antagonism of residual mivacurium-induced block may not be applicable to patients in whom the above TOFC intervals are markedly prolonged.

Second, there is ample evidence that edrophonium is less efficacious than neostigmine when antagonizing deep levels of neuromuscular block induced by nondepolarizing agents of intermediate and long duration.[14,15] As Beemer *et al.* pointed out,[16] reversal time is determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery by the neuromuscular blocking agent, with the latter becoming the major determinant at profound levels of block. Anticholinesterases have a "ceiling" to the extent of the block that can be completely antagonized. When reversal of neuromuscular block greater than this ceiling (T1 < 30%) is attempted, the peak effect of the antagonist is followed by a slow plateau phase, which represents the balance between diminishing anticholinesterase activity and spontaneous recovery of neuromuscular block. Because of edrophonium's faster onset at small degrees of block, when direct antagonism of the block by an anticholinesterase is the predominant process determining reversal time, edrophonium produces faster recovery than neostigmine. At profound levels of block, neostigmine has the shorter onset time. Because the primary aim of this investigation was to see whether small doses of edrophonium significantly shortened recovery time, attempting antagonism at TOFC-1 or -2 did not seem to be a productive approach.

The amount of time that can be "saved" by antagonism of residual mivacurium-induced block at threshold TOFC-4 is limited, because the average TOFC-4 to TOF >0.70 interval is only 10.7 min. Because the peak effect of edrophonium usually is evident in about 2 min, the maximum theoretical reduction possible in the time to a TOF ratio of 0.70 is <9 min. We found that administration of 0.3 mg/kg edrophonium resulted in shortening this time interval by about 7 min. Increasing the dosage 2.5-fold produced little additional advantage. Naguib *et al.*[2] reported similar results when attempting to reverse mivacurium at 90% twitch depression. They found that 1.0 mg/kg edrophonium produced no improvement in T1 or TOF ratios 10 min after reversal compared to 0.4 mg/kg edrophonium.

The extent to which the dosage of edrophonium can be reduced further is as yet undetermined. In this regard, however, an abstract by Bryson *et al.* is of interest.[17] They administered mivacurium by infusion (average duration 1 h) at electromyographic T1 values of 10% to 40 patients. On completion of the infusion, patients either were allowed to recover spontaneously

or were given 0.125, 0.25, or 0.50 mg/kg edrophonium. Average time to spontaneous return of a TOF value ≥0.70 was 14.3 min, and this was reduced by 4.5, 4.4, and 5.6 min, respectively, by the three doses of edrophonium. These authors could not demonstrate any advantage in increasing the dose of edrophonium beyond 0.15 mg/kg.

Clinical Recommendations

In patients in whom the TOFC-1–3 or TOFC-2–4 intervals lie close to the norm, the decision to avoid reversal with an anticholinesterase frequently will be rational. If, despite normal indexes of recovery, a decision to accelerate the drug's offset is made, we believe the optimal approach to reversal of mivacurium may differ from what many anesthesiologists consider standard practice.

First, we believe that edrophonium probably is the anticholinesterase of choice for antagonizing the effects of mivacurium. Because neostigmine's peak effect occurs 7–11 min after administration,[18] any time saved *versus* spontaneous recovery is likely to be small. Neostigmine has no proven advantages over edrophonium in terms of speeding the drug's rate of recovery. There are theoretic reasons and experimental evidence to suggest that attempts to antagonize profound neuromuscular block with neostigmine may be counterproductive. Cook *et al.* demonstrated that neostigmine but not edrophonium inhibits the *in vitro* degradation of mivacurium when incubated with human plasma.[19] Although this effect may be of little consequence once significant recovery from mivacurium has occurred, the situation may be different if antagonism is attempted in the absence of a visual or palpable response to TOF stimulation. Kao *et al.*[20] demonstrated this difference dramatically. They compared time to recovery from the termination of a mivacurium infusion to a TOF ratio of 0.90 in three groups in which profound neuromuscular block (98–99% T1 depression) was maintained. In group 1, recovery was allowed to proceed spontaneously. Patients in groups 2 and 3 received 0.07 mg/kg neostigmine and 1.0 mg/kg edrophonium, respectively, at the end of the infusion. Spontaneous recovery took 17.9 min, and edrophonium administration reduced this by 5.6 min. However, in individuals who received neostigmine, the recovery period was almost twice (32.4 min) that seen with spontaneous recovery. Hence, if Kao's work can be duplicated by others, it appears that neostigmine should be avoided when attempting to antagonize profound mivacurium-induced blockade. In addition, it seems less than elegant to administer an anticholinesterase whose cholinergic effects may last 60–90 min to antagonize the effects of a relaxant with an elimination half-life of 2–2.5 min.

Second, we suggest that, at some point in the anesthetic administration, the TOFC-1–3 or TOFC-2–4 interval be measured. A normal response assures the existence of adequate plasma cholinesterase activity. Based on our data and that of others,[16] when reversing mivacurium-induced blockade, it appears there is no logical reason to administer doses of edrophonium in excess of 0.5 mg/kg. In fact, doses of 0.3 mg/kg or less may prove equally efficacious. Additional studies of the efficacy of smaller dose of edrophonium for reversal of the residual effects of mivacurium seem warranted.

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