RECOVERY CHARACTERISTICS FOLLOWING ANTAGONISM OF ATRACURIUM WITH NEOSTIGMINE OR EDROPHONIUM

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SUMMARY
The evoked reversal characteristics of atracurium were studied in 21 patients using edrophonium or neostigmine and a train-of-four pattern of stimulation. Reversal of residual atracurium-induced neuromuscular blockade was significantly more rapid using edrophonium compared with neostigmine. The ratio of the fourth twitch in the train-of-four to the first twitch—the T4 ratio—was significantly greater when the first twitch (T1) had recovered to 75% of control Ti, using edrophonium compared with neostigmine. A T4 ratio of 0.5 was confirmed to be compatible with the reliable and safe reversal of atracurium-induced neuromuscular blockade.

Although a single twitch may have returned to its control value after spontaneous or evoked recovery from neuromuscular agents, marked train-of-four fade may remain and indicate a significant degree of residual receptor occupancy (Ali et al., 1981). Thus, the train-of-four pattern of stimulation has been advocated as the preferred technique for monitoring the degree of neuromuscular blockade (Lee and Katz, 1977). Edrophonium is a synthetic, reversible acetylcholinesterase inhibitor. It is now established that in larger than hitherto customary doses—500 µg kg⁻¹ or more—it is able to produce reliable and sustained antagonism of neuromuscular blocking agents (Cronnelly, Morris and Miller, 1982). We have studied the evoked reversal characteristics of atracurium using edrophonium and compared them with those obtained following neostigmine.

PATIENTS AND METHODS
After Ethics Committee approval and informed consent, 21 unpremedicated adults (ASA class I) were studied. Anaesthesia was induced with thiopentone administered through an indwelling needle in the dorsum of the right hand after which control train-of-four recordings were obtained. Atracurium 0.25 mg kg⁻¹ was administered (preceded and followed by the injection of 1 ml of physiological saline). The trachea was intubated and anaesthesia maintained with nitrous oxide and 1% enflurane in 33% oxygen. Ventilation was controlled using a Bain-type coaxial breathing system and a fresh gas flow calculated to maintain normocapnia.

Neuromuscular transmission was monitored by stimulating the left ulnar nerve at the wrist with surface electrodes using supramaximal 0.2-ms impulses in a train-of-four pattern at 2 Hz, repeated every 12 s (Myotest). The evoked twitch of the adductor pollicis muscle was measured using a Grass force-displacement transducer (FT03C) and Devices recorder. The hand and forearm were immobilized in a special arm board for the recording of thumb adduction, to ensure comparability of results.

At the end of surgery the T4 ratio, defined as the ratio of the amplitude of the fourth evoked response to the amplitude of the first response in the same train, was determined. Patients were excluded from further study if (a) our standard criterion for satisfactory spontaneous reversal from neuromuscular blockade—a T4 ratio of 0.5—had been attained, (b) no evoked twitch at all could be demonstrated indicating an unquantifiable degree of residual blockade or (c) if incremental doses of atracurium had been administered. Residual neuromuscular blockade was reversed by randomly allocating patients to receive either edrophonium 500 µg kg⁻¹ or neostigmine 40 µg kg⁻¹, together with atropine. Patients continued to inhale nitrous oxide, 33% oxygen and 1% enflurane until all measurements were complete. The following were noted: height of the first twitch in the train-of-four (T1) compared with the control T1, before reversal; time taken from the administration of the antagonist to achieve a T4 ratio of 0.5; time taken from a T4 ratio of 0.25 to one of 0.5; and the T4 ratio when T1 had recovered to 75% of control T1.

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Statistical analysis used unpaired, two-tailed t-tests with \( P < 0.001 \) being defined as highly significant.

**RESULTS**

The results are summarized in table I. The degree of spontaneous recovery before administration of the antagonist was not significantly different in the two groups. Evoked reversal of atracurium to a \( T_4 \) ratio of 0.5 was significantly \((P < 0.001)\) more rapid using edrophonium compared with neostigmine. Similarly, the time taken to recover from a \( T_4 \) ratio of 0.25 to one of 0.5 after antagonist administration was also significantly \((P < 0.001)\) more rapid following edrophonium. After evoked reversal of atracurium to a \( T_1 \) of 75% of control, the \( T_4 \) ratio was significantly \((P < 0.001)\) greater following the administration of edrophonium compared with that following neostigmine.

**DISCUSSION**

Edrophonium is a reversible acetylcholinesterase inhibitor. Previously thought of as being too short-acting to produce sustained antagonism of neuromuscular blocking drugs (Koelle, 1975) it is now established that, when it is given in doses of 500 \( \mu \text{g kg}^{-1} \), reliable sustained antagonism can be achieved (Bevan, 1979; Kopman, 1979; Cronnelly, Morris and Miller, 1982). Cronnelly, Morris and Miller (1982) have also shown that the duration of antagonism produced by edrophonium 500 \( \mu \text{g kg}^{-1} \) is similar to neostigmine 43 \( \mu \text{g kg}^{-1} \). In addition, edrophonium is known to have a more rapid onset than neostigmine when antagonizing tubocurarine (Cronnelly, Morris and Miller, 1982) or vecuronium (Baird, Bowman and Kerr, 1982). Our results confirm that evoked reversal from atracurium-induced neuromuscular blockade is significantly more rapid when using edrophonium compared with neostigmine (figs 1, 2). As well as being a mathematically significant result, this was obvious clinically.

In addition, it has been demonstrated that, for a given degree of evoked recovery of the first twitch in the train-of-four, there was significantly less \( T_4 \) fade present when using edrophonium compared with neostigmine (figs 1, 2). The significance of this observation depends to a large extent upon the possible mechanisms involved in \( T_4 \) fade. Bowman (1980) believes that single twitch depression, and tetanic or train-of-four fade, are the result of the interaction of acetylcholine antagonists with different binding sites within the neuromuscular junc-

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**TABLE I. Summary of results (mean values ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine ((n = 11))</th>
<th>Edrophonium ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_1 ): control ( T_1 ) before reversal</td>
<td>0.37 ± 0.19</td>
<td>0.43 ± 0.11</td>
</tr>
<tr>
<td>Time to ( T_4 ) ratio of 0.50 (s)</td>
<td>205.4 ± 78.7</td>
<td>36.0 ± 18.0</td>
</tr>
<tr>
<td>Time from ( T_4 ) ratio of 0.25 to ( T_4 ) ratio of 0.50 (s)</td>
<td>108.0 ± 31.2</td>
<td>18.2 ± 11.3</td>
</tr>
<tr>
<td>( T_4 ) ratio when evoked recovery of ( T_1 ) is 75% of control ( T_1 )</td>
<td>0.37 ± 0.10</td>
<td>0.64 ± 0.07</td>
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</tbody>
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Fig. 1. Evoked reversal of residual neuromuscular blockade using edrophonium 500 \( \mu \text{g kg}^{-1} \) (tracing of original recording). C = control train-of-four recording. E = point at which edrophonium was administered. The train-of-four recordings are at 12-s intervals. In the penultimate train-of-four recording, \( T_1 \) has recovered to 75% of control \( T_1 \) and the \( T_4 \) ratio is 0.64.
ANTAGONISM OF ATRACURIUM

tion, and reviews the possible mechanisms for the phenomenon of fade. These, he suggests, are first, a prejunctional effect in which neuromuscular blocking drugs act at presynaptic nicotinic receptors, or perhaps other sites, in such a way that the mobilization of acetylcholine is impaired. Thus, during high frequency stimulation, transmitter output becomes exhausted so that fade occurs. Second, it is possible that high frequency stimulation causes acetylcholine antagonists to exert a different postjunctional effect in such a way that this becomes more pronounced as the stimulation continues. Bowman argues that, although there is evidence in support of and against both possibilities, the weight of evidence is in favour of a prejunctional mechanism. Standaert (1982) has also reviewed possible pre- and postsynaptic effects of neuromuscular blocking agents and suggests that these drugs do not necessarily act by blocking pre-synaptic nicotinic cholinceptors, but rather that they decrease the release of transmitter from rapidly stimulated nerve endings because they block open sodium channels and thereby interfere with mobilization. Whatever the precise mechanism for $T_4$ fade, it seems certain that neuromuscular blocking drugs act at a number of sites within the neuromuscular junction and that this array of actions is responsible in some way for $T_4$ fade.

Different acetylcholine antagonists are also thought to have their own emphasis of action at these various sites. Williams, Webb and Calvey (1980) demonstrated that pancuronium, alcuronium, tubocurarine, fazadinium and gallamine produced their own characteristic degree of $T_4$ fade, such that pancuronium was associated with relatively less $T_4$ fade for any given amount of $T_1$ depression, than gallamine. They concluded that their results may be reflecting different affinities or intrinsic activities of the five drugs for prejunctional and postjunctional receptors. Our results suggest that, whatever the spectrum of activity of atracurium within the neuromuscular junction, edrophonium has a more complete range of reversal characteristics than neostigmine.

The fact that edrophonium is able to antagonize atracurium and other non-depolarizing drugs more rapidly than neostigmine, and has greater train-of-four fade antagonist properties, may be interlinked. Neostigmine and edrophonium are both synthetic reversible anticholinesterases with a quaternary ammonium structure. However, there is a fundamental difference in the structure of edrophonium compared with that of neostigmine and other synthetic compounds such as pyridostigmine, or the naturally occurring compounds such as physostigmine. Edrophonium lacks the carbamyl group which interacts with the esteratic site of acetylcholinesterase. The carbamyl–ester linkage of neostigmine is hydrolysed by acetylcholinesterase so that, with time, a structure similar to edrophonium is formed, consisting of a quaternary ammonium group and a pyridyl nucleus. It might be speculated that the train-of-four fade antagonist properties of anticholinesterases are more in the moiety of the molecule. That is, edrophonium or the structurally similar hydrolysed portion of the neostigmine molecule, are in some way the more active antagonists of neuromuscular blocking drugs at the sites within the neuromuscular junction responsible for train-of-

![Fig. 2. Evoked reversal of residual neuromuscular blockade using neostigmine 40 μg kg⁻¹ (tracing of original recording). C = control train-of-four recording. N = point at which neostigmine was administered. The degree of spontaneous recovery before antagonist administration is similar to figure 1. The breaks in the baseline after antagonist administration each represent 60 s. In the third train-of-four recording after control, $T_1$ has recovered to 75% of control $T_1$ and the $T_4$ ratio is 0.32.](image-url)
four fade, be these postjunctional or prejunctional. We believe that it would be premature to interpret our results as demonstrating that edrophonium has more marked prejunctional effects, until the mechanisms involved in train-of-four fade are more precisely known.

Another feature of this study was the reliability of a $T_4$ ratio of 0.5 in predicting adequate evoked (or spontaneous) recovery from neuromuscular blockade produced by atracurium. All patients were observed in a recovery area for at least 3 h and standard tests of adequate reversal were applied, such as sustained head lift for 5 s. There was no evidence of recurarization and all patients could perform sustained head-lift and cough vigorously. It has been emphasized (Ali et al., 1981) that reliance on the return of the single twitch to the control value, as a criterion of return of normal function, may be misleading. Marked train-of-four or tetanic fade may still be present, indicating a significant degree of residual receptor occupancy. Lee and Katz (1977) have pointed out that tetanus facilitates the neuromuscular response during and following its application so that it will artificially shift all subsequent neuromuscular events toward normality. As a result, they have suggested that train-of-four monitoring is the preferred technique for assessing the degree of residual neuromuscular blockade.

We conclude that, compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and that edrophonium antagonizes more rapidly residual atracurium-induced neuromuscular blockade. We also suggest that a $T_4$ ratio of 0.5 provides reasonable evidence of safe reversal from residual atracurium-induced neuromuscular blockade.

REFERENCES
CARACTERISTICAS DE RECUPERACION DESPUES DEL ANTAGONISMO DEL ATRACURIO CON NEO-ESTIGMINA O EDROFONIO

SUMARIO
Se llevaron a cabo estudios respecto de las características de inversión evocada del atracurio en 21 pacientes al usar edrofonio o neo-estigmina y un método de tren-de-cuatro para estimulación. La inversión del bloqueo neuro-muscular residual inducido por atracurio fue bastante más rápida con el edrofonio que con la neo-estigmina. La relación de la cuarta contracción en el tren-de-cuatro con la primera contracción —la relación $T_4$— fue mucho más alta cuando la primera contracción ($T_1$) había recuperado hasta un 75% del control de $T_1$ al usar edrofonio y en comparación con la neo-estigmina. Una relación de $T_4$ de 0,5 confirmó ser compatible con la inversión confiable y segura del bloqueo neuro-muscular inducido por atracurio.