DETERMINANTS OF THE REVERSAL TIME OF COMPETITIVE NEUROMUSCULAR BLOCK BY ANTICHOLINESTERASES

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SUMMARY
We have assessed, in 200 patients, the determinants of the reversal time of competitive neuromuscular block by anticholinesterase when alcuronium and atracurium neuromuscular block were antagonized by neostigmine 0.04 and 0.08 mg kg\(^{-1}\) and edrophonium 0.5 and 1.0 mg kg\(^{-1}\). A biexponential relationship was found between the reversal time (time from injection of anticholinesterase to a train-of-four ratio of 70%) and the degree of neuromuscular block at reversal (all groups; \(F\) ratio, \(P < 0.05\)). Reversal time was determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery of the neuromuscular blocking agent, with the latter becoming the major determinant at profound levels of neuromuscular block (0–10% of control twitch height). Neostigmine, in the doses studied, appeared to have a higher “ceiling” of neuromuscular block which it completely antagonized, although edrophonium had a more rapid onset of action. The reversal time for alcuronium became progressively longer relative to atracurium as neuromuscular block increased because of the slower spontaneous recovery rate. Avoidance of profound neuromuscular block at the completion of surgery is required to ensure reliable antagonism of the block within 5–10 min by an anticholinesterase. Neostigmine 0.08 mg kg\(^{-1}\) was found to be the most effective agent in antagonizing profound neuromuscular block.

KEY WORDS

PATIENTS AND METHODS
We studied 200 patients undergoing general anaesthesia (table I). The study was approved by the hospital Ethics Committee. Patients were allocated to receive neostigmine 0.04 mg kg\(^{-1}\) and atropine 0.02 mg kg\(^{-1}\), neostigmine 0.08 mg kg\(^{-1}\) and atropine 0.03 mg kg\(^{-1}\), edrophonium 0.5 mg...
TABLE I. Patient characteristics and drugs received

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium 0.5 mg kg⁻¹</td>
<td>12/13</td>
<td>24-76</td>
<td>68.3 (11.7)</td>
</tr>
<tr>
<td>Alcuronium (n = 25)</td>
<td>13/12</td>
<td>24-78</td>
<td>72.0 (14.6)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>8/17</td>
<td>17-73</td>
<td>67.6 (14.7)</td>
</tr>
<tr>
<td>Edrophonium 1.0 mg kg⁻¹</td>
<td>12/13</td>
<td>19-73</td>
<td>66.4 (17.8)</td>
</tr>
<tr>
<td>Alcuronium (n = 25)</td>
<td>9/16</td>
<td>19-72</td>
<td>67.0 (15.2)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>9/16</td>
<td>19-76</td>
<td>67.4 (11.2)</td>
</tr>
<tr>
<td>Neostigmine 0.04 mg kg⁻¹</td>
<td>9/16</td>
<td>17-78</td>
<td>67.3 (13.0)</td>
</tr>
</tbody>
</table>

with no resting tension and wrapped in a warm towel. The EMG was calibrated after induction of anaesthesia, but before the administration of any neuromuscular blocking agent, by establishing a control twitch height to the first stimulus of a TOF stimulation (100 % T1c) and a TOF ratio of the first to the fourth response (T1:T4). Muscle paralysis was produced initially with suxamethonium or a bolus dose of atracurium or alcuronium and maintained thereafter with the competitive neuromuscular blocking agent. The anaesthetic technique was chosen by the responsible anaesthetist in accordance with standard clinical practice. Table II details the anaesthetic data for the different neuromuscular blocking agent–anticholinesterase groups.

At the end of the surgical procedure, residual neuromuscular block was antagonized by an anticholinesterase, the drug and dose depending on the group to which the patient was allocated. T1:T4 = 70 % was defined as indicating adequate clinical recovery from neuromuscular block [9]. A continuous recording was made of the first and fourth twitch response of the EMG from time of administration of the anticholinesterase to recovery. The first twitch response of the EMG at time of administration of the anticholinesterase (%T1.reversal) and the time taken from injection of the anticholinesterase to T1:T4 greater than 70 % (reversal time) were noted. Anaesthesia was discontinued thereafter, but EMG monitoring continued as long as possible. The first twitch response of the EMG at this time (%T1.recovery) was recorded.

Allowance for drift in calibration of the EMG

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Anaesthesia V/I</th>
<th>Duration (min)</th>
<th>Suxamethonium (n)</th>
<th>Dose of blocking drug (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium 0.5 mg kg⁻¹</td>
<td>24/1</td>
<td>110 (53)</td>
<td>11</td>
<td>18.0 (6.4)</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>19/6</td>
<td>108 (58)</td>
<td>5</td>
<td>60.3 (29.2)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>22/3</td>
<td>85 (30)</td>
<td>8</td>
<td>16.5 (3.2)</td>
</tr>
<tr>
<td>Neostigmine 0.04 mg kg⁻¹</td>
<td>23/2</td>
<td>88 (39)</td>
<td>13</td>
<td>17.7 (5.9)</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>19/6</td>
<td>81 (34)</td>
<td>10</td>
<td>42.7 (15.2)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>24/1</td>
<td>86 (48)</td>
<td>8</td>
<td>17.0 (5.2)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>18/7</td>
<td>112 (71)</td>
<td>8</td>
<td>54.0 (29.0)</td>
</tr>
</tbody>
</table>
ANTAGONISM OF NEUROMUSCULAR BLOCK

Atracurium

Alcuronium

First twitch at reversal (% T1 reversal/T1 recovery)

First twitch at reversal (% T1 reversal/T1 recovery)

FIG. 1. Biexponential relationship between reversal time (time from injection of the anticholinesterase until a train-of-four ratio of 70%) and the degree of neuromuscular block at time of administration of the anticholinesterase (first twitch height %T1.reversal/T1.recovery) for antagonism of atracurium and alcuronium by edrophonium 0.5 mg kg⁻¹ (---) and 1.0 mg kg⁻¹ (....) and neostigmine 0.04 mg kg⁻¹ (-----) and 0.08 mg kg⁻¹ (---) (in each case inclusion of the biexponential regression line; F ratio, $P < 0.05$).

was made by taking %T1.recovery as the control first twitch height [10]. Using this criterion, the depth of neuromuscular block at reversal was %T1.reversal/T1.recovery. Patients were excluded from the study if excessive drift in the EMG calibration had occurred as indicated by a %T1.recovery of less than 60% T1c.

Curve fitting was performed with the extended least squares computer software MK-MODEL (Elsevier-BIOSOFT). The curves of reversal time vs depth of neuromuscular block at time of administration of the anticholinesterase for the different groups were fitted with mono- and biexponential curves. The justification for inclusion of the second exponential was tested with the $F$ ratio, $P < 0.05$ [11].

Patient and anaesthetic data were compared with ANOVA and chi-square analysis. Three way-ANOVA and unpaired Student's $t$ test with Bonferroni correction for multiple comparisons were used to compare reversal data at profound and light block. $P < 0.05$ was defined as significant. Data are presented as mean (SD).

RESULTS

The biexponential relationships between reversal time and the degree of neuromuscular block at time of administration of the anticholinesterase are illustrated in figure 1 for antagonism of atracurium and alcuronium neuromuscular block by edrophonium 0.5 and 1.0 mg kg⁻¹ and by neostigmine 0.04 and 0.08 mg kg⁻¹. This biexponential relationship was consistent with reversal time being determined by two processes. A second slower process became a determinant of the reversal time at more profound levels of neuromuscular block.

Analysis of the individual EMG recordings of antagonism of neuromuscular block by anticholinesterase showed that edrophonium had an initial peak effect within 1–3 min, and thereafter recovery occurred at a slow rate during a plateau phase. In contrast, neostigmine produced a more gradual and sustained antagonism, with the plateau phase discernible only after 6–10 min. Figure 2 illustrates typical recordings of the antagonism of an alcuronium-induced neuromuscular block by neostigmine 0.04 mg kg⁻¹ and edrophonium 0.5 mg kg⁻¹. The plateau phase was absent when small degrees of block were antagonized. The plateau phase was discernible in the antagonism of deep neuromuscular block (0–10% T1.reversal/T1.recovery) in patients from all groups. The rate of recovery of alcuronium neuromuscular block during the plateau phase was slower and more variable than that of atracurium. Figure 3 illustrates an example of very slow recovery of alcuronium neuromuscular block during the plateau phase following antagonism of the block by edrophonium 0.5 mg kg⁻¹ (data from this patient were not included in other analyses because recovery was not recorded until T1:T4 > 70%).
Table III details the reversal time for antagonism of profound (0–10% \( T1.\text{reversal}/T1.\text{recovery} \)) and light (> 30% \( T1.\text{reversal}/T1.\text{recovery} \)) neuromuscular block for the different neuromuscular blocking agent–anticholinesterase groups. There were significant differences between the reversal times at both profound and light block for neuromuscular blocking agents, anticholinesterases and doses (in each case, three-way ANOVA, \( P < 0.05 \)).
The administration of anticholinesterase did not induce neuromuscular block in any patient. In patients administered anticholinesterase at almost complete spontaneous recovery of the neuromuscular block, the block quickly recovered and remained at T1:T4 > 70% with EMG monitoring continuing for up to 25 min.

DISCUSSION

We have observed a biexponential relationship between the degree of competitive neuromuscular block and the time to adequate recovery following administration of an anticholinesterase. This biexponential relationship may be considered to reflect the differing contributions of the two major processes which determine the reversal time of a neuromuscular block. Direct antagonism of the block by the anticholinesterase was the primary process at small degrees of block (> 30 % T1.reversal/T1.recovery). Spontaneous recovery of the neuromuscular blocking agent was the predominant process determining reversal time at high degrees of neuromuscular block (0-10% T1.reversal/T1.recovery). The anticholinesterase had a “ceiling” to the extent of block which it could antagonize completely. When antagonism of degrees of neuromuscular block greater than the ceiling was attempted, the block continued to recover slowly during a plateau phase following the peak antagonistic effect of the anticholinesterase. This plateau represented a balance between spontaneous recovery and the waning antagonistic effect of the anticholinesterase. The duration of the antagonistic effect of edrophonium and neostigmine was a secondary determinant of the reversal time of deep neuromuscular block, as their duration of action was longer than that of the competitive neuromuscular blocking agents [2, 12-14].

The clinically significant difference in the reversal times of atracurium and alcuronium occurred at profound levels of neuromuscular block. The slower spontaneous recovery of alcuronium caused the reversal times for alcuronium to increase relative to atracurium. The recovery time (time for spontaneous recovery of neuromuscular block from 25% to 75% of control twitch height) for an intubating dose of atracurium is 20 min and is relatively independent of the size of the dose [13]. The recovery time for an intubating dose of alcuronium is 45 min and may increase to 112 min or longer after repetitive doses because of its cumulative properties [14, 15]. The reversal time of profound neuromuscular block following repetitive doses of alcuronium may be extremely prolonged. The reversal characteristics of alcuronium and atracurium may be considered as generally representative of long and intermediate acting competitive neuromuscular blocking agents [1-8]; the superior antagonizing characteristics of intermediate acting neuromuscular blocking agents explains the observed lower incidence of residual block associated with their use [16].

The anticholinesterases edrophonium and neostigmine have important differences in their ability to antagonize competitive neuromuscular block. The faster onset of antagonism by edrophonium in the present study is consistent with
the observations of times to peak antagonism of a tubocurarine block of 0.8–2.0 min for edrophonium 0.5 mg kg⁻¹, and 7–11 min for neostigmine 3 mg/70 kg [2, 12]. Hence at small degrees of block, when antagonism of the block by an anticholinesterase was the predominant process determining reversal time, edrophonium produced a shorter reversal time than neostigmine. At profound levels of neuromuscular block the converse applied, with neostigmine having a shorter reversal time. This may reflect the administration of a larger effective dose of neostigmine. The dosage of neostigmine relative to edrophonium is difficult to compare, as their dose–response curves are not parallel [2, 16]. Alternatively, this may be a reflection of the supposed greater efficacy of neostigmine [17]. The shorter reversal times of profound block by neostigmine may also be a reflection of its longer duration of action [2, 12].

The effect of dose of anticholinesterase on reversal time is complex. Dosage determines the ceiling of neuromuscular block which the anticholinesterase can directly antagonize. Increasing the dose of edrophonium from 0.5 to 1.0 mg kg⁻¹ increased the ceiling of neuromuscular block which it could antagonize directly. The dose of anticholinesterase may be important also in determining the reversal time of small degrees of block, below the ceiling of the anticholinesterase, for anticholinesterases which have a slow onset of action. Increasing the dose of neostigmine from 0.04 to 0.08 mg kg⁻¹ decreased the reversal time of low levels of block. By determining the duration of antagonism, the dosage of anticholinesterase may affect also the reversal time of block deeper than the ceiling of the anticholinesterase. Theoretically, the effect of dosage in this circumstance would be most pronounced with edrophonium, because of its shorter duration of action.

Concern about the administration of large doses of anticholinesterases inducing muscle weakness, particularly when antagonizing agents of intermediate duration of action such as atracurium at almost complete spontaneous recovery of the neuromuscular block, appears to be largely unfounded. An increase in tetanic fade has been observed after repeat administration of neostigmine 2.5 mg in the presence of a block which had fully recovered [18]. The significance of minor degrees of tetanic fade is difficult to assess, as fade may occur in the absence of neuromuscular blocking agents [19]. In this and other studies, in which neuromuscular block was assessed with TOF stimulation, there has been no evidence of muscle weakness being induced by an anticholinesterase, even when it was administered at near total recovery of the block [20, 21].

Understanding the processes which govern the reversal time of a competitive neuromuscular block by an anticholinesterase is the best way to ensure adequate recovery in all patients and avoid the potential complications of residual paralysis. The anaesthetist cannot rely on a given dose of an anticholinesterase to ensure rapid antagonism of a competitive block at the termination of surgery. The most important determinant of reversal time is the depth of neuromuscular block at the time of antagonism and this should determine the anticholinesterase and its dose. Another factor which should be considered is the type and dose of competitive neuromuscular blocking agent. When large doses of long acting competitive neuromuscular blocking agents are administered during surgery, it may be anticipated that antagonism of profound block by an anticholinesterase will be prolonged.

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REFERENCES


