Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium

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Summary
We have studied the train-of-four (TOF) response mechanomyographically during onset of neuromuscular block produced by subclinical doses of suxamethonium in order to follow the augmentation of the first twitch of the TOF (T1) and TOF fade compared with control TOF responses before the drug was given. In the groups given suxamethonium 0.05, 0.1, 0.2 and 0.3 mg kg$^{-1}$, the increments in T1 after administration of the drug were observed before twitch depression occurred; these were mean 22.3 (SEM 8.1) %, 19.2 (3.3) %, 10.8 (2.0) % and 4.2 (2.2) %, respectively. This effect was more marked with the lower doses ($P<0.05$). The degree of TOF fade was moderate during onset of neuromuscular block and depended on the dose of drug. The results of this study suggest that low doses of suxamethonium produced transient increase in muscle tension and twitch depression with significant TOF fade. We conclude that suxamethonium was associated with presynaptic effects as a consequence of brief stimulation of acetylcholine release followed by progressive diminution at the neuromuscular junction. (Br. J. Anaesth. 1997; 79: 379–381).

Key words
Neuromuscular block, suxamethonium. Neuromuscular block, measurement of response.

It is generally accepted that suxamethonium acts on postjunctional structures causing depolarizing block. This block is the result of opening of cation channels by activation of acetylcholine receptors on the $\alpha$ subunits of the postsynaptic receptor pentamer. However, some investigators have produced evidence that the drug may act on both pre- and postsynaptic receptor sites at the neuromuscular junction.$^1$ The presynaptic effect of a large amount of acetylcholine is to produce a transient increase in muscle tension because of postsynaptic stimulation followed by depression of neuromuscular transmission as a consequence of inhibition at presynaptic receptors at motor nerve endings.$^2$ The fade of rain-of-four (TOF) response is accepted as a consequence of the presynaptic effect resulting from progressive diminution of the output of acetylcholine.$^3$ Therefore, we have investigated the simultaneous appearances of these two responses induced by subclinical doses of suxamethonium.

Methods and results
Approval for this study was obtained from the Ethics Committee of Soon Chun Hyang University Hospital. We studied 48 healthy adult patients, ASA I or II, undergoing elective surgery and not suffering from any neuromuscular, renal or hepatic diseases, or receiving any medication which might influence neuromuscular transmission. Patients with a personal or family history of suxamethonium apnoea or malignant hyperthermia were excluded.

Patients were given glycopyrronium 0.2 mg and nalbuphine 10 mg i.m., 1 h before induction of anaesthesia. Approval for this study was obtained from the Ethics Committee of Soon Chun Hyang University Hospital. We studied 48 healthy adult patients, ASA I or II, undergoing elective surgery and not suffering from any neuromuscular, renal or hepatic diseases, or receiving any medication which might influence neuromuscular transmission. Patients with a personal or family history of suxamethonium apnoea or malignant hyperthermia were excluded.

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After thiopentone 4–5 mg kg$^{-1}$ for induction, anaesthesia was maintained with 66% nitrous oxide in oxygen with increments of thiopentone or fentanyl 1 $\mu$g kg$^{-1}$, or both, as required. Ventilation of the lungs was assisted using a face mask, when necessary, to maintain normocapnia. The patient’s core temperature was maintained within the normal range. In this study, subclinical doses of suxamethonium were used in order to measure the effect on twitch height and TOF, because it is difficult to obtain TOF responses during the short onset time of...
Table 1  Twitch response data (mean (SEM)) for each subclinical dose of suxamethonium. T1 or T4 = First or fourth twitch height of the train-of-four (TOF), TOF ratio = T4/T1 at first TOF response during onset on neuromuscular block after drug administration and at its corresponding twitch height level during recovery. Means with different letters (A, B, C, D) indicate significant differences between groups for each variable (P<0.05, Student–Newman–Keuls). *P<0.05 compared with recovery (paired Student’s t test).

<table>
<thead>
<tr>
<th>Suxamethonium (mg kg⁻¹)</th>
<th>0.025</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
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<tbody>
<tr>
<td>Twitch T1 augmentation (%)</td>
<td>—</td>
<td>22.3 (8.1)A</td>
<td>19.2 (3.3)A</td>
<td>10.8 (2.0)B</td>
<td>4.2 (2.2)B</td>
<td>—</td>
</tr>
<tr>
<td>Maximum depression (%)</td>
<td>—</td>
<td>5.5 (2.5)A</td>
<td>60.6 (3.2)B</td>
<td>93.4 (1.0)C</td>
<td>98.5 (0.7)C</td>
<td>99.5 (0.5)C</td>
</tr>
<tr>
<td>TOF ratio (T4/T1, %) during onset</td>
<td>91.7 (1.4)A</td>
<td>76.5 (1.0)A</td>
<td>70.3 (1.4)AC</td>
<td>68.7 (1.8)AC</td>
<td>68.6 (1.7)AC</td>
<td>—</td>
</tr>
<tr>
<td>94.9 (1.1)</td>
<td>91.9 (1.2)</td>
<td>95.4 (1.2)</td>
<td>95.6 (1.9)</td>
<td>92.5 (1.9)</td>
<td></td>
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<tr>
<td>Recovery</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>94.9 (1.1)</td>
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<td>95.4 (1.2)</td>
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Neuromuscular block induced by clinical doses of suxamethonium. After induction of anaesthesia, twitch height of the TOF was allowed to stabilize for at least 10 min and patients were allocated according to randomly selected numbers to receive one of the following subclinical doses of suxamethonium: 0.025, 0.05, 0.1, 0.2, 0.3 or 0.4 mg kg⁻¹ i.v. via an indwelling needle at the wrist. Eight patients received each dose.

Neuromuscular recording was continued to measure the following: (1) twitch augmentation (%), defined as the maximum increase in T1 compared with control T1; (2) maximum T1 depression (%), defined as the greatest depression of T1 after injection; and (3) change in TOF ratio (%). This was calculated from the first TOF ratio at the depressed height of T1 during onset after injection and at the corresponding height level of T1 during recovery.

Statistical analysis was performed using SPSS. Results were compared using Kruskal–Wallis one-way analysis of variance (ANOVA) and groups which differed significantly by ANOVA were tested with Student–Newman–Keuls multiple range test to determine difference between groups. The TOF ratio during onset was compared with that during recovery in each group using the paired Student’s t test. Differences were considered statistically significant at P<0.05. Data are reported as mean (SEM).

Twitch augmentations of TOF responses after drug administration were observed before depression of T1 and were greatest for T1 for the four twitch responses of TOF: 22.3 (8.1) %, 19.2 (3.3) %, 10.8 (2.0) % and 4.2 (2.2) % in the groups given suxamethonium 0.05, 0.1, 0.2 and 0.3 mg kg⁻¹, respectively. This effect was more marked with the lower dose (P<0.05) (table 1) and was not observed in groups given 0.025 and 0.4 mg kg⁻¹. Partial depression occurred in groups given suxamethonium 0.05, 0.1 and 0.2 mg kg⁻¹ and almost complete T1 depression occurred in groups given 0.3 and 0.4 mg kg⁻¹. However, there were no changes in TOF response in the suxamethonium 0.025 mg kg⁻¹ group. The degree of TOF fade at the first TOF during onset after drug administration was moderate: 76.5 (1.0) %, 70.3 (1.4) %, 68.7 (1.8) % and 68.6 (1.7) % in the groups given suxamethonium 0.1, 0.2, 0.3 and 0.4 mg kg⁻¹, respectively. TOF fade depended on the dose of drug given. Almost sustained TOF responses occurred during recovery and TOF fade during onset of neuromuscular block was significantly greater than that at the corresponding height of T1 during recovery from neuromuscular block (P<0.05) (table 1).

Comment

It is thought that there are at least two populations of presynaptic cholinergic receptors, each subserving different physiological functions: one group is the presynaptic nicotinic receptor which acts as a positive feedback and responds to low concentrations of acetylcholine causing an autofacilitatory effect. This is believed to be mediated partly through its action on synapsin I causing an increase in the immediately available store of acetylcholine increasing the rate of release of acetylcholine after motor nerve activity. The second group is the presynaptic muscarinic receptor which acts as a negative feedback and responds to high concentrations of acetylcholine. Stimulation of these receptors causes reduced release of transmitter in the presence of motor nerve activity. This would explain the response observed experimentally after a large dose of acetylcholine is injected directly into the arterial supply of a muscle; initial powerful contraction is followed by transient neuromuscular block. There is convincing evidence of a physiological mechanism of this type causing an initial positive feedback via autoreceptors on the nerve endings and then negative feedback limiting the effect of the high concentration released. As suxamethonium produces an acetylcholine-like action, it has been proposed that neuromuscular block by this drug is the result of both pre- and postsynaptic sites of action. We have demonstrated that twitch augmentation produced by suxamethonium was apparent in the groups given doses which only partially depress T1 and it was absent in the groups given doses which were either too small to cause block or too large. The results could be explained by proposing that suxamethonium causes brief stimulation of intact presynaptic receptors on motor nerve endings increasing the mobilization of acetylcholine. Any effect is overwhelmed by a large dose which causes complete block. Therefore, it seems likely that suxamethonium, which in some respects resembles acetylcholine, may initially evoke activation of presynaptic cholinergic receptors which augments depolarization of the postsynaptic membrane. Its action then progresses to cause...
TOF fade is generally attributed to a presynaptic effect caused by progressive decrease in acetylcholine release from the nerve endings. Presynaptic binding of neuromuscular blocking agents prevents rapid acetylcholine mobilization required to maintain adequate acetylcholine release during rapid stimulation, such as during TOF or tetany. The generally accepted view is that the degree of fade is related to the propensity for presynaptic binding and demonstration of fade can be taken as evidence of presynaptic block of a feedback mechanism. Full depolarizing block induced by suxamethonium is characterized by lack of fade but repeated doses or continuous infusion of drug produces neuromuscular block characterized by tetanic fade, termed phase II block. However, in our study, despite administration of subclinical, small doses of suxamethonium, the TOF response appeared to be associated with approximately 70% TOF fade during onset of block; even during recovery from block, TOF fade did not occur. Otherwise, it is presumed that the moderate fade of TOF response during onset after subclinical doses of suxamethonium results from incomplete block of presynaptic receptors and the sustained TOF response during recovery should result from rapid dissociation from presynaptic sites by enzymatic hydrolysis at the early stage of recovery. However, the different effects observed on TOF fade and T1 depression may be caused by different affinities and rates of binding for pre- and postsynaptic receptors at the neuromuscular junction.

The results of this study suggest that the hypothesis that, although the site of action of suxamethonium is postsynaptic it also has a presynaptic site of action, may be true, but clinically it is masked by large doses.

Acknowledgements

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References