FADE PROFILES DURING SPONTANEOUS OFFSET OF NEUROMUSCULAR BLOCKADE: VECURONIUM AND GALLAMINE COMPARED

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It has been noted that different neuromuscular blocking drugs are associated with varying degrees of fade when neuromuscular block is monitored with repetitive or high frequency stimulation (such as train-of-four (TOF) or tetanic stimulation). The majority of previous studies have observed and reported the degree of fade during the onset of blockade [1,2]. The characteristic "fade profiles" of individual myoneural blockers have been ascribed to their varying affinities for pre- and postsynaptic receptors [1,3] and has led to the suggestion that neuromuscular blocking drugs and their antagonists may be matched in terms of their pre- and postsynaptic activity [4].

However, the degree of fade occurring during the onset of blockade may not be the same as during offset [3,5-7], when antagonists are administered. We have studied the degree of TOF fade during spontaneous offset, as well as onset, for gallamine and vecuronium—agents which are thought to have widely varying degrees of pre- and postsynaptic activity [1-3,8].

PATIENTS AND METHODS

After local ethics committee approval, 30 patients (ASA class I and II) scheduled to undergo elective surgery requiring the use of neuromuscular blocking drugs gave their informed consent to inclusion in this study. All patients were within 20% of their ideal weight. Patients with neuromuscular, hepatic or renal disease were excluded, as were any patients receiving medications known to influence neuromuscular transmission. The non-dominant arm was immobilized in a splint and used for electromyographic monitoring (Datex Relaxograph) utilizing the ulnar nerve at the wrist and the hypothenar muscles for positioning of the stimulating and recording electrodes. A TOF pattern of stimulation with supramaximal 0.1-ms square wave impulses was used, and repeated every 20 s.

A standardized, but not randomized, anaesthetic technique was used. Patients were either unpremedicated or they received diazepam 10 mg by mouth approximately 1 h before operation. Anaesthesia was induced with thiopentone 4–6 mg kg⁻¹ after fentanyl 1 μg kg⁻¹ had been injected through an indwelling needle to a vein on the dorsum of the dominant hand. The patient spontaneously breathed 66% nitrous oxide in
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Oxygen with 1% inspired halothane delivered via a Bain type coaxial breathing system and facemask. Baseline neuromuscular recordings were obtained and when they were stable, approximately equipotent doses (ED₉₅) of either vecuronium (0.05 mg kg⁻¹) or gallamine (2.0 mg kg⁻¹) were injected through the same needle, preceded and flushed with 1 ml of physiological saline. The neuromuscular blocking drugs were injected at the same rate, as a rapid bolus. Tracheal intubation was performed when the first twitch of the train (T₁) was 5% of control or after 4 min, whichever was sooner. Anaesthesia was maintained with 66% nitrous oxide and 0.5% inspired halothane in oxygen plus incremental doses of fentanyl as indicated. Intermittent positive pressure ventilation utilized a Nuffield 200 series anaesthesia ventilator and Bain type circuit with fresh gas flow of 70 ml kg⁻¹ min⁻¹.

A complete record of twitch height was obtained during onset, spontaneous offset and after the administration of the anticholinesterase. Two indices of neuromuscular blockade were recorded: the height of T₁ compared with control T₁ (T₁: control %) and the ratio of the height of the fourth to the height of the first response in the same train (T₄ ratio). The records were judged to be suitable for analysis if T₁ following evoked reversal was 90–110% of control T₁. Comparisons of fade between drugs were made at the T₁ value nearest to 25% of control (T₁: control 25%) during onset and at 25, 50 and 75% of control (T₁: control 25, 50 and 75%) during spontaneous offset.

Table I. Demographic data of the patients

<table>
<thead>
<tr>
<th></th>
<th>Vecuronium</th>
<th>Gallamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>5/6</td>
<td>4/4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>mean (SD)</td>
<td>30(14)</td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>19–70</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>mean (SD)</td>
<td>64(9)</td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>52–75</td>
</tr>
</tbody>
</table>

The results are expressed as mean (± SD). Statistical analysis utilized non-parametric methods (Wilcoxon's rank sum test or Wilcoxon's signed rank test), as appropriate.

RESULTS

Although 30 patients were studied, the records for only 11 patients receiving vecuronium and eight patients receiving gallamine were suitable for analysis based on the described criterion. The demographic data are shown in Table I.

During the onset of neuromuscular blockade, at T₁:control 25%, the T₄ ratio was 0.47 (0.09) in the vecuronium group and 0.13 (0.11) in the gallamine group (fig. 1). The degree of fade was significantly greater with gallamine than with vecuronium (P < 0.01).

The times to return to all chosen offset T₁:control values were much longer in the gallamine group: for example, T₁:control 50% for gallamine was 98 (50) min compared with 18 (3) min for vecuronium.

Comparisons of fade at T₁:control 25% during onset and spontaneous offset of neuromuscular blockade showed significantly (P < 0.01) more fade during offset than during onset with both vecuronium and gallamine. The T₄ ratios for vecuronium (fig. 1) were 0.47 (0.09) during onset of blockade and 0.06 (0.09) during offset. The results for the gallamine group demonstrated a similar pattern, with a T₄ ratio of 0.13 (0.11) during onset and 0.04 (0.06) during spontaneous offset.

When the T₄ ratios were compared during early spontaneous offset at T₁:control 25% and 50%, there were no significant differences between the two myoneural blockers. The T₄ ratio for the gallamine group at T₁:control 25% was 0.04 (0.06) compared with 0.06 (0.09) for the vecuronium group. When T₁ had returned to 50% of control, the T₄ ratio for the patients receiving gallamine was 0.13 (0.06) and 0.12 (0.07) for the patients receiving vecuronium. However, during late spontaneous offset, when T₁ had returned to 75% control (fig. 1), the use of gallamine was associated with significantly (P < 0.05) less fade, having a T₄ ratio 0.33 (0.07) compared with a T₄ ratio 0.21 (0.08) for vecuronium.

DISCUSSION

It has been suggested that non-depolarizing neuromuscular blocking drugs inhibit neuromuscular transmission by acting at a number of sites within the neuromuscular junction, not just at the classical postjunctional nicotinic acetylcholine receptor [9–15]. It has also been suggested that fade occurring during the TOF or tetanus is
one manifestation of the action of neuromuscular blockers at various sites within the neuromuscular junction. One explanation is that depression of the single twitch is explained by the action of the neuromuscular blocker at the postjunctional receptor, but that fade represents interaction with the prejunctional site.

Individual neuromuscular blocking drugs have been thought to have characteristic patterns of activity at the neuromuscular junction because of their varying affinity for pre- and postsynaptic sites and are thus associated with their own fade profile [1, 2, 8]. In this study we have investigated two neuromuscular blocking drugs thought to act at either end of the fade spectrum. Williams, Webb and Calvey [1] using electromyography, showed a marked degree of fade associated with the onset of blockade with gallamine, an observation which we confirmed. In contrast, vecuronium was associated with most fade, pancuronium with less and vecuronium with least fade. Indeed, it was suggested [2] that, because vecuronium was associated with so little fade, if lack of fade was used as the sole criterion for antagonism of blockade, patients could be left with significantly impaired muscle strength in the postoperative period. This work was performed on horses. Our study has confirmed previous findings in man and in terms of the degree of fade during the onset of gallamine- and vecuronium-induced block. (Gallamine showing a marked degree of fade during onset: at T1: control 25% the T4 ratio was 0.13 (0.11), compared with 0.47 (0.09) with vecuronium.)

Bowman [3] has demonstrated the variable relationship between the degree of fade during onset and offset, suggesting that the prejunctional receptors were isoreceptors of the postjunctional receptors with different pharmacological profiles. This explains the different affinities and rates of binding for the different myoneural blocking drugs. A slower rate of binding to these fade sites would explain the observation that depression of twitch and fade develop and recover with different time courses. He showed, in cats, the greater degree of fade during offset with vecuronium. These findings have been confirmed in man using vecuronium and atracurium [7]. Our present study confirms the findings of Pearce, Casson and Jones [7] with vecuronium, and shows that this is also true with gallamine.

However, when the two drugs are compared during spontaneous offset, as opposed to onset,
we have demonstrated that they appear to have similar degrees of fade up to T1:control 75% when the situation is reversed, with gallamine being associated with less fade than vecuronium.

Pearce, Casson and Jones [7] demonstrated that the degree of TOF fade during the onset of blockade depends upon the dose of myoneural blocking drug administered, with larger doses being associated with less fade. To exclude this effect in this study, we administered approximately equipotent (ED_{95}) doses—vecuronium 0.05 mg kg^{-1} and gallamine 2.0 mg kg^{-1}. As both drugs were administered on a weight-related basis, we included only patients within 20% of their ideal weight. The possible effects of cumulation resulting from an incremental technique were avoided in this study by administering only a bolus dose of neuromuscular blocking drug. For this reason we felt unable to randomize the administration of the chosen drug and gallamine was given for procedures which were anticipated to last for a minimum period of 1 h. There was thus a difference in the age of the two groups, with the gallamine group having a mean age 53 yr compared with 30 yr in the vecuronium group. Although the gallamine group were older, they were not elderly, and patients were included only if they had normal blood biochemistry suggesting no abnormality of excretion and presumably normal duration of action.

It should be noted that we utilized the integrated hypothenar electromyogram (as recorded by the Datex Relaxograph) and, although the results may not be strictly comparable with studies in which electro- or mechanomyography of the thenar muscles have been used, it is known that there is a good correlation between the different recording methods [16,17].

Results were included only if T1, after evoked reversal, returned to within 10% of control values. Thirty studies were performed, but only 19 achieved suitable results. In the 11 rejected recordings, T1 failed to reach 90% of control in nine and, in two, T1 increased to values greater than 110% after antagonism. Viby-Mogensen [18], in a review of the evoked electromyographic response, also noted that the response often did not return to 100% control during recovery. It is so far not known whether this is the result of technical problems such as changes in electrode impedance or position or, as Paloeheim and Rantala [19] have suggested, it might be attributable to the disappearance of central enhancement of the evoked EMG response when the patient falls asleep.

In conclusion, we have demonstrated that gallamine and vecuronium are associated with significantly different degrees of TOF fade during onset (gallamine > vecuronium). However, during early spontaneous offset (T1 up to 50% of control) their fade profiles are similar and, during late spontaneous offset (T1:control 75%), the situation is vecuronium > gallamine. Thus conclusions and assumptions previously made concerning the fade profiles of neuromuscular blocking drugs (and hence their pre- and postsynaptic effects), especially if based on work performed during the onset of neuromuscular blockade only, may not be valid.

REFERENCES


