FADE CHARACTERISTICS AND ONSET TIMES FOLLOWING ADMINISTRATION OF PANCURONIUM, TUBOCURARINE AND A MIXTURE OF BOTH AGENTS

J. N. CASHMAN, R. M. JONES AND L. M. VELLA

Potentiation of neuromuscular blockade when mixtures of certain non-depolarizing agents are administered has been demonstrated in vitro (Pollard and Jones, 1983) and in vivo (Wong, 1969). Although the overall speed of onset of neuromuscular blockade has been extensively investigated, few studies have specifically measured other facets of the onset characteristics of myoneural blockers. This study was designed to investigate the onset characteristics of pancuronium, tubocurarine and a mixture of both of these agents, in terms of:

1. Depression of the first twitch in the train-of-four.
2. The degree of train-of-four fade.
3. The latent, manifest and total onset times.

PATIENTS AND METHODS

The study was approved by the hospital Ethics committee and 24 ASA class I patients of either sex scheduled to undergo routine surgical procedures gave their informed consent to inclusion. Their ages ranged from 19 yr to 46 yr, and their weights from 42 kg to 80 kg; no patient of greater than 10% above ideal weight was included in the study. Patients were allocated at random to one of three groups to receive tubocurarine 0.6 mg kg\(^{-1}\), pancuronium 0.1 mg kg\(^{-1}\), or a mixture of these two relaxants (pancuronium 0.05 mg kg\(^{-1}\) plus tubocurarine 0.3 mg kg\(^{-1}\)).

Anaesthesia was induced with thiopentone 200—400 mg and maintained with nitrous oxide in oxygen delivered via a Bain type coaxial breathing system and face mask, with additional 50-mg increments of thiopentone administered as needed. The non-dominant arm was immobilized in a splint and the ulnar nerve stimulated at the wrist via surface electrodes connected to a Myotest nerve stimulator delivering train-of-four supramaximal square wave pulses at 2 Hz of 0.2 ms duration repeated every 10 s. The evoked force of contraction of the adductor pollicis muscle was measured by a Grass force displacement transducer connected to a Devices preamplifier and chart recorder.

After control readings had been obtained, the neuromuscular blocking drug was injected i.v. to
Fig. 1. Summary of indices measured.

the contralateral arm and flushed by a fast running infusion. T1 depression (reduction in the height of the first twitch (T1) in the train-of-four relative to control T1) and the reduction in the T4 ratio (height of the fourth twitch (T4) relative to the height of T1) were recorded. Three features of onset time were derived from the recordings: total onset time was defined as the time from injection of the myoneural blocking drug to a 90% reduction in T1; latent onset time was defined as the time from injection of the myoneural blocker to the first clearly (> 5%) reduced T1; and manifest onset time was defined as the time from the first clearly reduced T1 to 90% T1 depression (Minsaas and Stovner, 1980). We also measured fractional manifest onset times to 50% and 75% T1 depression (fig. 1). All measurements were completed before the commencement of surgery.

All results are expressed as mean (SD) and statistical analysis was performed using unpaired Student's t test.

RESULTS

The three groups were comparable in respect of age, weight and pre-induction haemodynamic values (table I). One patient was excluded from statistical analysis as a result of a violation of the experimental programme, thus seven patients received tubocurarine, seven received pancuronium and nine received the mixture.

During the onset of neuromuscular blockade, at 75% T1 depression tubocurarine was associated with significantly more T4 fade than was either pancuronium (P < 0.05) or the mixture of pancuronium and tubocurarine (P < 0.01) (table II); the degree of T4 fade at 75% T1 depression was identical for pancuronium and the mixture of pancuronium and tubocurarine (0.61). In addition, T1 depression at the point when the fourth twitch disappeared was significantly greater following tubocurarine than following pancuronium (P < 0.01), or the mixture (P < 0.01) (table III). Again, these values were identical for pancuronium and the mixture of pancuronium and tubocurarine (6%). Furthermore, the equations for the regression lines of T1 depression v. T4 ratio for pancuronium and the mixture were very similar, but differed from that for tubocurarine (fig. 2).

| Tubocurarine | 13 (4)* |
| Pancuronium | 6 (3) |
| Mixture | 6 (2) |

| Tubocurarine | 0.81 (0.07) | 0.70 (0.10) | 0.41 (0.18)* |
| Pancuronium | 0.80 (0.05) | 0.72 (0.04) | 0.61 (0.18)* |
| Mixture | 0.81 (0.03) | 0.75 (0.05) | 0.61 (0.09) |

*Significantly more fade than pancuronium (P<0.05) or the mixture (P<0.01)
It can be seen (table IV, fig. 3) that pancuronium had a longer and more variable latent onset time than either tubocurarine or the mixture, but tubocurarine, although having an initially more rapid manifest onset time (to 50% T1 depression), had a longer overall manifest onset time (to 75% and 90% T1 depression); the onset time curves of pancuronium and of tubocurarine cross at about 80% twitch depression. The mixture had the shortest latent onset time, but thereafter behaved in a manner almost identical to that of pancuronium. It thus had a faster overall total onset time and achieved 90% twitch depression more rapidly than either drug on its own, although these differences were not statistically significant.

**TABLE IV. Latent, manifest and total onset times for the three drug regimens**

<table>
<thead>
<tr>
<th>Onset times (s)</th>
<th>Neuromuscular blocking drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tubocurarine</td>
</tr>
<tr>
<td>Latent</td>
<td>41.3 (19.1)</td>
</tr>
<tr>
<td>Manifest to:</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>14.0 (10.5)</td>
</tr>
<tr>
<td>75%</td>
<td>53.5 (37.7)</td>
</tr>
<tr>
<td>90%</td>
<td>94.0 (56.3)</td>
</tr>
<tr>
<td>Total to:</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>55.2 (28.2)</td>
</tr>
<tr>
<td>75%</td>
<td>94.8 (55.9)</td>
</tr>
<tr>
<td>90%</td>
<td>135.1 (73.5)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

It is likely that single twitch depression and train-of-four fade represent the interaction of neuromuscular blocking drugs at different sites within the neuromuscular junction (Bowman, 1980). Although there is still some disagreement, a site other than the post-synaptic cholinoreceptor, possibly situated presynaptically, would seem likely to be responsible for fade.

We have demonstrated that both pancuronium and the mixture of pancuronium and tubocurarine, in the doses outlined, are associated with very similar degrees of T4 fade when onset of neuromuscular blockade reaches 75% T1 depression, and that
tubocurarine alone is associated with significantly more fade. Williams, Webb and Calvey (1980) also observed that tubocurarine was associated with significantly more fade during onset than was pancuronium. However, it is noteworthy that the fade characteristics of our mixture were identical (at 75% T1 depression) with those of pancuronium alone; this was an unexpected observation. On the assumption that a pre-synaptic receptor is responsible for fade, tubocurarine would appear to have less affinity for these receptors in the presence of pancuronium.

The presence of pancuronium in a mixture with tubocurarine modified the effect of tubocurarine on T1 depression also. It would appear that the presence of one drug may alter the affinity of the other for the receptor responsible for T1 depression, for the receptor responsible for T4 fade, or for both. Interactions between neuromuscular blocking drugs are also reflected in a comparison of onset times of the individual drugs with those of the mixture.

We excluded several factors which influence the speed of onset achieved with neuromuscular blocking agents: the dose administered, the effect of inhalation anaesthetic agents (Auer and Meltzer, 1914; Pollard and Miller, 1973), increasing age (Feldman, 1976), obesity (Vaughan, 1974) and variation in haemodynamic parameters (Feldman, 1976; Goat et al., 1976). We did not admit to the study any patient older than 50 yr, and thus have investigated a younger group of patients, with apparently normal circulation times as suggested by their pre-induction haemodynamic values. No patient of greater than 10% above ideal weight was included in the study. The potential effect of inhalation agents was eliminated by avoiding their use during the period when neuromuscular blockade was being studied. Thus, the onset times—latent, manifest and total—can be expected to reflect the characteristics of the individual agents used. In these circumstances the present study appears to demonstrate that:

1. Tubocurarine has a shorter latent onset time than pancuronium.
2. Pancuronium has a more variable latent onset time.
3. Pancuronium has an overall more rapid manifest onset time.

Consequently, the onset curves of tubocurarine and pancuronium cross at a T1 depression of approximately 80% (fig. 3).

The marked variability in latent onset observed with pancuronium (Blackburn and Morgan, 1978; Minsaas and Stovner, 1980; Williams, Webb and Calvey, 1980) and the crossing over of the onset curves of pancuronium and tubocurarine (Blackburn and Morgan, 1978), are findings which have been noted by other workers also. The precise significance of the latter observation remains unclear, although it may be the result of a differential rate of penetration into the synaptic cleft by the individual agents (Waud, 1967; Blackburn and Morgan, 1978; Hull, 1982). Although the differences in onset time in our study did not achieve statistical significance, our result for the total onset time of pancuronium 0.1 mg kg\(^{-1}\) is within 10% of the values obtained by other investigators (Blackburn and Morgan, 1978; Minsaas and Stovner, 1980). The mixture of pancuronium with tubocurarine appears to have the more rapid latent onset time of tubocurarine, and the more rapid manifest onset time of pancuronium and, thus, a total onset time which is more rapid than either drug alone. This might be anticipated, given the association between dose of neuromuscular blocking drug and speed of onset, and the fact that mixtures of pancuronium and tubocurarine have been shown to be synergistic (Duncalf et al., 1983; Pollard and Jones, 1983).

In conclusion, we have shown that mixtures of neuromuscular blocking drugs do not necessarily have onset characteristics which are simply a composite of the individual agents. This suggests that, within the neuromuscular junction, the site(s) or mechanism(s) of action of an individual neuromuscular blocker may be altered by the presence of another blocking agent. This may, in part at least, explain the observed differences in the latent, manifest and total onset times of the mixture of pancuronium and tubocurarine compared with those of the individual agents. That the total onset time of neuromuscular blockade may be reduced by administering mixtures of neuromuscular blocking drugs may have clinical significance.

REFERENCES


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