DIFFERENTIAL EFFECTS OF NEUROMUSCULAR BLOCKING AGENTS ON SUXAMETHONIUM-INDUCED FASCICULATIONS AND MYALGIA

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Suxamethonium commonly produces a number of undesirable effects, including muscle fasciculations, postoperative myalgia, and transient hyperkalaemia. These phenomena are commonly modified by pretreatment with small doses of non-depolarizing neuromuscular blockers. Suxamethonium produces muscle fasciculations by combining with neuronal cholinceptors, causing prejunctional depolarization [1]; in these conditions, local axon reflexes initiate the release of acetylcholine from the terminals of motor units. The relationship between fasciculations and postoperative myalgia is controversial. Electromyographic evidence suggests that muscle pain is related to the rate of firing of motor units, but not to visible fasciculations [2]. Non-depolarizing myoneural blockers may modify fasciculations and muscle pain by preventing prejunctional depolarization and local axon reflexes, thus decreasing the rate of motor unit firing. They have multiple sites of action at the neuromuscular junction [3]; our previous studies suggested that gallamine has predominantly presynaptic effects, in comparison with pancuronium [4]. Pretreatment with these neuromuscular blocking drugs may therefore have differential effects on suxamethonium-induced fasciculations and myalgia. Other drugs, including small doses of suxamethonium itself, have also been used to prevent these complications [5]. However, the effectiveness of this procedure is a matter of controversy.

SUMMARY

The effect of pretreatment with suxamethonium, gallamine or pancuronium on suxamethonium-induced fasciculations and myalgia was studied in a controlled, randomized and double-blind clinical trial. Both fasciculations and myalgia were assessed on a four-point rating scale. There was no significant correlation between fasciculations and postoperative muscle pain at 24, 48 or 72 h, and pretreatment with suxamethonium had no significant effect on fasciculations or myalgia. Gallamine had a more marked effect on fasciculations than pancuronium, and the decrease in the fasciculation score was statistically significant. In contrast, pancuronium had a greater effect on myalgia, and decreased postoperative muscle pain significantly at 24 and 48 h. These differences may reflect the differential activity of gallamine and pancuronium at the neuromuscular junction. Pretreatment had little or no effect on plasma potassium concentrations.

The effects of pretreatment on suxamethonium-induced fasciculations and myalgia have been widely studied. Nevertheless, few previous attempts have been made to analyse these phenomena in the context of a controlled clinical trial. In this study, we have assessed the effectiveness of pretreatment with suxamethonium, gallamine or pancuronium, in a controlled, randomized and double-blind clinical trial.

PATIENTS AND METHODS

Sixty identical 1.1-ml ampoules containing 0.9% saline, suxamethonium 10 mg ml⁻¹, gallamine 20 mg ml⁻¹ or pancuronium 1 mg ml⁻¹ were prepared by the Pharmacy Manufacturing Department of
the Royal Liverpool Hospital. Similar doses of suxamethonium and gallamine have been used in many previous studies [5-7]. The doses of pancuronium 1 mg and gallamine 20 mg were considered to have equipotent effects on neuromuscular transmission. The ampoules were randomized, using random sampling numbers [8] by one of us (T.N.C.) who had no subsequent connection with the trial. The ampoules were sealed in sequentially numbered envelopes, and administered in this order to the patients who were entered to the trial.

Sixty female subjects (ASA grade I) aged 18-66 yr were studied. There was no significant difference between the ages and the body weights of the patients in the four treatment subgroups. All the patients had been admitted to hospital for elective plastic, ENT or gynaecological surgery. Informed consent was obtained, and the trial was approved by the local Ethics Committee. Patients were routinely premedicated with nitrazepam 10 mg during the previous evening and diazepam 5 mg three times on the day of surgery. Anaesthesia was induced with thiopentone 3 mg kg\(^{-1}\) i.v. and the sequentially numbered pretreatment was given. After 45 s a further dose of thiopentone 1 mg kg\(^{-1}\) i.v. and suxamethonium 1.5 mg kg\(^{-1}\) i.v. was administered. No other blocking agents were used, and patients were subsequently allowed to breathe spontaneously oxygen, nitrous oxide and enflurane from a Magill circuit. Blood was removed for the measurement of plasma potassium concentrations immediately before, and 5 min after, the induction of anaesthesia. The presence and degree of fasciculations were assessed on a four-point rating scale: 0 = no visible fasciculations; 1 = extremely fine muscular movements; 2 = minimal contractions of the trunk, face and extremities; 3 = vigorous contractions of the trunk, face and extremities.

Postoperative myalgia was assessed on a four-point rating scale at 24, 48 and 72 h, using the following criteria: 0 = no muscle pain; 1 = slight muscle pain; 2 = moderate muscle pain; 3 = severe muscle pain.

All the patients were ambulant within 24 h of surgery. The effects of the pretreatments on muscle fasciculations and postoperative myalgia were compared by Wilcoxon's signed rank test.

![Graph showing the effects of saline, suxamethonium, gallamine and pancuronium on fasciculations and postoperative myalgia.](http://bja.oxfordjournals.org/)

**Table I. Effects of pretreatment with saline, suxamethonium, gallamine or pancuronium on fasciculations and postoperative myalgia. Figures represent median values (interquartile ranges). The data were compared by Wilcoxon's signed rank test.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fasciculation score</th>
<th>Myalgia score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Saline</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.5*</td>
<td>0.8</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.9</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

The correlation between these variables was not statistically significant (r = -0.081; P > 0.05).
Plasma potassium concentrations were compared by the analysis of variance.

RESULTS

In the 60 patients studied, there was no correlation between the fasciculation score and postoperative muscle pain at 24 h (fig. 1), 48 h or 72 h. Some patients had a high fasciculation score and a low myalgia score; others had a low fasciculation score and a high myalgia score. Pretreatment with suxamethonium had no significant effect on the fasciculation score or the myalgia score at 24, 48 or 72 h (table I). In contrast, gallamine significantly decreased the fasciculation score when compared with pretreatment with saline (from a median value of 1.3, to 0.5). Although postoperative myalgia scores were also decreased at 24, 48 and 72 h, these differences were not statistically significant. Pancuronium also decreased the fasciculation score, but to a lesser extent than gallamine (table I); nevertheless, it had a more marked effect on myalgia, and the decrease in postoperative muscle pain at 24 and 48 h was statistically significant (table I).

Moderately difficult or difficult intubation was commoner after pretreatment with gallamine or pancuronium (table II). Plasma potassium concentrations were not significantly affected by any of the pretreatments (table III). Saline and suxamethonium produced no change in concentration, while gallamine and pancuronium caused a slight decrease in plasma potassium concentrations.

DISCUSSION

This study was designed as a double-blind controlled trial of the effects of pretreatment with suxamethonium, gallamine or pancuronium on suxamethonium-induced fasciculations and postoperative myalgia. In practice, this aim was not entirely realized. As reported by previous authors [5, 6, 9, 10], a variable proportion of patients develop fasciculations after pretreatment ("self-taming") with suxamethonium. In the present study, this phenomenon was observed in two patients; it was not considered to invalidate the results of the investigation.

In this study, there was a delay of 45 s between pretreatment and the subsequent administration of suxamethonium. This latent period was shorter than the time interval in most other studies involving pretreatment with non-depolarizing neuromuscular blockers. Although many previous studies have used a latency of 1–3 min, there is no unequivocal evidence that this delay is required. Our previous studies suggested that both gallamine and pancuronium usually produce 50% neuromuscular blockade within 2 min [4]. Since suxamethonium itself requires approximately 1 min to produce comparable effects, it was considered that an interval of 45 s between pretreatment and the administration of suxamethonium was adequate.

Muscle fasciculations did not correlate significantly with postoperative myalgia at 24, 48 or 72 h. Some patients had marked fasciculations and no subsequent muscle pain, while others had no fasciculations, but developed severe myalgia. These results are generally consistent with previous studies [9, 11–13].
Pretreatment with suxamethonium had no significant effect on muscle fasciculations; we were unable to confirm that their incidence was decreased, as reported by other authors [5, 9]. Similarly, postoperative myalgia at 24, 48 and 72 h was not decreased when compared with control subjects [9, 10].

It is generally accepted that gallamine and pancuronium decrease both muscle fasciculations and postoperative myalgia [11, 14, 15]. Nevertheless, in this study the two non-depolarizing neuromuscular blocking drugs appeared to have differential effects on these phenomena. Gallamine had a more marked effect on fasciculations than pancuronium, and the decrease in the fasciculation score was statistically significant. In contrast, pancuronium had a greater effect on myalgia, and significantly decreased postoperative muscle pain at 24 and 48 h. Other authors have suggested that gallamine is more effective than pancuronium in preventing muscle fasciculations [14, 16]. We propose that these differences may reflect the differential activity of gallamine and pancuronium at the neuromuscular junction. Gallamine may preferentially affect fasciculations by preventing prejunctional depolarization and local axon reflexes, and thus decrease the rate of motor unit firing. In contrast, the predominantly postsynaptic effects of pancuronium may mainly modify postoperative myalgia. In the U.K., gallamine is commonly used for pretreatment, since it is miscible with thiopentone and has a short duration of action; our results suggest that, although it may effectively prevent fasciculations (and by corollary, muscle movement during intubation), it is less effective than pancuronium in the suppression of postoperative myalgia.

In this study, moderately difficult or difficult intubation was commoner after pretreatment with gallamine or pancuronium, as anticipated from the results of other authors [16, 17]. Pretreatment with saline and “self-taming” had no effect on serum potassium concentrations immediately after administration of suxamethonium. The absence of hyperkalaemia may reflect the timing of the post-induction sample [17, 18]; however, in patients with peripheral denervation or burns, the maximal increase in serum potassium concentration occurs at 4–5 min [19, 20]. As shown in other studies, pretreatment with non-depolarizing myoneural blockers causes a slight decrease in plasma potassium concentrations within 5 min of the administration of suxamethonium [17].

In conclusion, this study suggests that non-depolarizing neuromuscular blocking agents with mainly presynaptic or postsynaptic effects may have differential effects on suxamethonium-induced fasciculations and myalgia. The development of blocking drugs with selective pre- and postsynaptic actions on neuromuscular transmission may well have different effects on these phenomena.

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REFERENCES