GLYCOPYRRONIUM REQUIREMENTS FOR ANTAGONISM
OF THE MUSCARINIC SIDE EFFECTS OF EDROPHONIUM†

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The reversible cholinesterase inhibitor edrophonium, in doses of 0.5 mg kg\(^{-1}\) or greater, has a more rapid onset of effect than neostigmine, together with a lower incidence of muscarinic side effects [1]. Cronnelly, Morris and Miller [2] showed that the atropine requirements of edrophonium are 50% of those of neostigmine.

Previous studies comparing atropine and glycopyrronium as anticholinergics for use with edrophonium, concluded that the former was the agent of choice. However, in these studies glycopyrronium was administered simultaneously with edrophonium [3,4]. Mirakhur and colleagues showed that glycopyrronium has a slower time to peak effect than atropine [5].

The aim of this study was to define a dosage and administration sequence of glycopyrronium with edrophonium which would minimize cardiovascular changes during the antagonism of competitive neuromuscular blockade using this combination.

PATIENTS AND METHODS

Sixty adult patients, ASA I or II, requiring general anaesthesia for elective surgery were studied. Local Ethics Committee approval was obtained, and all patients gave informed consent. No patient was receiving medication affecting

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clinically indicated. Following completion of surgery, residual neuromuscular blockade was antagonized using one of the edrophonium–glycopyrronium combinations. The glycopyrronium was supplied in coded ampoules containing either 100 µg ml⁻¹ or 200 µg ml⁻¹, and administered as 0.5 ml of solution per 10 kg body weight. The investigating anaesthetist was unaware of the dosage regimen to which the patient was allocated, although he was not blinded as to timing of glycopyrronium administration. The facility existed to break the coding for an individual patient.

Cardiovascular data were collected 2 min before administration of glycopyrronium, during the administration, and at 1-min intervals for the 10 min afterwards. During this period anaesthesia and artificial ventilation were maintained with halothane and nitrous oxide in oxygen. Continuous electrocardiographic display (CR5, Cardiac recorders Ltd, using lead CM5) provided information on heart rate and rhythm. Arterial pressure was measured non-invasively, using an automated oscillometric device (Dinamap 845, Critikon Ltd). Edrophonium 1.0 mg kg⁻¹ was administered either simultaneously with or at 1 min following glycopyrronium, depending upon the group to which the patient was allocated.

Oropharyngeal secretions were suctioned before administration of the antagonizing mixture, and again before tracheal extubation. The secretions at this stage were graded by the anaesthetist as minimal, moderate or copious.

Statistical analysis of the cardiovascular data was performed using repeated measure analysis of variance. Demographic and other data were analysed for significant differences between the groups using analysis of variance, Fisher's exact test or chi-square test, as appropriate.

RESULTS

The patients were comparable with respect to demographic and control cardiovascular data, taken 2 min before administration of glycopyrronium (table I). No statistically significant differences were detected in the distribution of premedicant drugs or incidence of fentanyl administration between the groups. Comparison of control heart rates between the patients who received temazepam and those who received papaveretum–hyoscine as premedication showed no significant differences.

Analysis of variance showed significant differences in heart rates between the groups (P < 0.001). Both groups given glycopyrronium 5 µg kg⁻¹ (groups B and D) showed greater stability of heart rate than the groups given 10 µg kg⁻¹. This larger dose of glycopyrronium, administered simultaneously with the edrophonium, produced an increase in heart rate of 30 beat min⁻¹ (95% confidence limits 28–32 beat min⁻¹) (fig. 1).

Figure 2 shows the distribution of patients in each group with heart rates less than 60 beat min⁻¹. In the group given glycopyrronium 5 µg kg⁻¹ simultaneously with edrophonium, seven patients had heart rates less than 60 beat min⁻¹ 1 min after administration of the antagonizing mixture, the slowest individual rate being 42 beat min⁻¹. Administering the dose of glycopyrronium before the edrophonium reduced this incidence; two patients developed rates slower than 60 beat

<p>| Table I. Demographic and control cardiovascular data (mean (SD)) |
|----------------------|----------------------|----------------------|----------------------|----------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>27.3 (8.2)</td>
<td>29.5 (13.0)</td>
<td>32.5 (11.4)</td>
<td>31.3 (12.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.4 (11.4)</td>
<td>66.8 (16.1)</td>
<td>65.4 (13.6)</td>
<td>62.5 (9.4)</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Premedication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Papaveretum–hyoscine</td>
<td>12</td>
<td>11</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>65.3 (11.5)</td>
<td>69.6 (16.2)</td>
<td>74.3 (17.0)</td>
<td>67.3 (10.5)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>114 (11.6)</td>
<td>119 (20.7)</td>
<td>118 (12.0)</td>
<td>115 (10.8)</td>
</tr>
</tbody>
</table>
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min\(^{-1}\) 1 min after the edrophonium, and the slowest rate was 50 beat min\(^{-1}\). The procedure required administration of further increments of glycopyrronium to correct a bradycardia of less than 40 beat min\(^{-1}\), or of less than 60 beat min\(^{-1}\) if accompanied by systemic hypotension. This intervention was not required in any of our patients.

Arterial pressure changes, following administration of the antagonizing mixtures, were small in all groups. There was no evidence of any significant differences between the groups, although the power to detect real differences between the groups in a trial of this size is only approximately 33%. However, the largest increase in systolic arterial pressure (seen in the group given glycopyrronium 10 µg kg\(^{-1}\) simultaneously with edrophonium) was only 15 mm Hg (95% confidence limits 13–17 mm Hg) greater than the control values.

The only arrhythmias noted were junctional rhythms. The incidence varied between 5 and 7 patients in each group. There were no significant differences between the groups.

There were no significant differences in the amount of oropharyngeal secretions between the groups (fig. 3), with even the lower doses of glycopyrronium providing acceptable control of

![Graph showing heart rate changes](image)

**Fig. 1.** Change in mean heart rate from control values in each of the four groups; glycopyrronium administered at time zero. Bar indicates the size of the 95% confidence interval for any of the points on the graph. Edrophonium administered at time zero or time 1 min, depending on group (see text).

![Graph showing oropharyngeal secretions](image)

**Fig. 3.** Anaesthetist’s assessment of oropharyngeal secretions. Black columns = minimal secretions; cross-hatched columns = moderate secretions.

![Graph showing patients with heart rates](image)

**Fig. 2.** Patients with heart rates less than 60 beat min\(^{-1}\). No patient in group C had a heart rate of less than 60 beat min\(^{-1}\).
secrections. Analysis of the amount of secretions between the temazepam and papaveretum-hyoscine premedicated patients in each of the groups showed no statistically significant differences.

**DISCUSSION**

The clinical relevance of haemodynamic changes produced by antagonism of neuromuscular blockade is not yet resolved, although Mostafa and Vucevic [6] demonstrated a significantly greater incidence of ST-segment depression in patients with cardiovascular disease who received atropine in place of glycopyrronium in combination with neostigmine. They postulated that this resulted from greater increases in the rate-pressure product in the patients who were given atropine. Similarly, Tse and colleagues [7] suggested that ST-segment depression detected in the anaesthetic recovery room might be associated with haemodynamic changes, particularly in heart rate, caused by antagonism of neuromuscular blockade. In the light of these studies, it seems logical to select anticholinergic–anticholinesterase combinations which minimize heart rate changes, especially in patients with ischaemic heart disease.

Previous investigators have suggested that simultaneous administration of atropine in a mixture with edrophonium to antagonize neuromuscular blockade provides greater cardiovascular stability than the simultaneous administration of glycopyrronium [3,4]. However, glycopyrronium may have other advantages over atropine; centrally acting anticholinergic drugs may be a factor in postoperative mental impairment. It is well established that anticholinergic drugs can impair memory [8] and a correlation between plasma concentrations of anticholinergic drugs and postoperative delirium has been described previously [9]. In addition, Simpson and colleagues [10] showed that patients who received atropine for premedication and antagonism of neuromuscular block showed postoperative memory impairment 2 days after surgery. Recovery from anaesthesia has been reported to be faster when glycopyrronium is used in place of atropine [11,12]. Based on these findings, the present study was designed to obtain a dosage and administration schedule for glycopyrronium with edrophonium to minimize cardiovascular changes during the antagonism of neuromuscular blockade.

Azar and colleagues [3] showed that glycopyrronium 0.5 mg (approximately 7 μg kg⁻¹) administered simultaneously with edrophonium 0.5 mg kg⁻¹ provided inadequate protection against early bradycardia. Mirakhur confirmed that the use of low doses (5 μg kg⁻¹) of glycopyrronium administered simultaneously with edrophonium 0.5 mg kg⁻¹ was often associated with a decrease in heart rate [4]. He showed further that increasing the dose of glycopyrronium to 10 μg kg⁻¹, whilst avoiding the initial bradycardia, was associated with the production of excessive tachycardia [4]. The use of atropine in a dose range of 10–14 μg kg⁻¹ was shown in both studies to provide more stable heart rates. This is in contrast to the previously described superiority of glycopyrronium over atropine as the antagonist of the muscarinic side effects of neostigmine [13].

Our results have confirmed these earlier studies. Additionally, we have demonstrated that the use of a low dose of glycopyrronium 5 μg kg⁻¹ administered before edrophonium minimizes the incidence and severity of the initial bradycardia, whilst avoiding later increases in heart rate. The distribution of premedicant drugs in each of the groups was comparable, and therefore did not introduce a source of bias.

Rupp and colleagues showed that edrophonium should be used in doses of 1.0 mg kg⁻¹ to provide rapid antagonism of profound competitive neuromuscular blockade [14]. Our results show that this dosage is not associated with an increase in anticholinergic requirement, and provide further confirmation of the weak muscarinic side effects of edrophonium. Further support is shown by the good control of oropharyngeal secretions with the lower doses of glycopyrronium. These findings differ from those of Engbaek and colleagues [15] who suggested that increased doses of atropine were required to accompany higher doses of edrophonium. However, in that study doses of up to 1.5 mg kg⁻¹ of edrophonium were used in association with very small doses of atropine.

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**REFERENCES**

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