ANTAGONISM OF THE MUSCARINIC EFFECTS OF EDROPHONIUM WITH ATROPINE OR GLYCOPRYRROLATE

A Comparative Study

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Although neostigmine is used widely to antagonize residual neuromuscular blockade edrophonium, in doses of 0.5 mg kg\(^{-1}\) or greater, has been suggested as an alternative because of its more rapid onset of action and lower incidence of muscarinic side-effects (Bevan, 1979; Kopman, 1979; Cronnelly, Morris and Miller, 1982).

Glycopyrrolate has been shown to be the anticholinergic agent of choice—in association with neostigmine—because of greater stability of heart rate and better control of secretions (Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Kongsrud and Sponheim, 1982). Cronnelly, Morris and Miller (1982) showed that the dose of atropine could be halved when it was mixed with edrophonium, but they did not include glycopyrrolate in their studies. Azar and his colleagues (1983) compared atropine and glycopyrrolate in a mixture with edrophonium at the doses commonly used with neostigmine, but did not assess the anticholinergic agents at lower doses.

In the present study, the efficacy of atropine at two doses in a mixture with edrophonium has been compared with that of glycopyrrolate administered similarly.

**PATIENTS AND METHODS**

After approval from the local ethics committee and informed patient consent, 100 adult patients (ASA grade 1) were studied. All were undergoing elective surgery requiring non-depolarizing neuromuscular blocking agents. They were premedicated with diazepam by mouth and anaesthetized with thiopentone i.v., nitrous oxide and 0.5–1.0% halothane in oxygen and fentanyl in doses of up to 3 \(\mu g\) kg\(^{-1}\) i.v. Atracurium or vecuronium were administered to provide neuromuscular blockade. Ventilation of the lungs was adjusted to maintain the end-tidal carbon dioxide concentration around 4.5–5.0%. Neuromuscular blockade was monitored using train-of-four (TOF) stimulation delivered from a peripheral nerve stimulator, the resultant force of thumb adduction being recorded on a neuromuscular function analyser (Myograph 2000). The detailed results of the effects of edrophonium on neuromuscular transmission are not included here and will be reported separately.

The last dose of fentanyl was administered at least 20 min before, and halothane discontinued about 10 min before, the end of surgery. The oropharynx was cleared of all secretions before administration of the test drugs.

The electrocardiogram (ECG) and arterial pressure were recorded continuously from 1 min before until 10 min after administration of the test mixture. Heart rate and arterial pressure were...
Table I. Patient characteristics and heart rate (mean±SEM) before antagonism

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Glycopyrrolate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10 µg kg⁻¹</td>
<td>20 µg kg⁻¹</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40±3.3</td>
<td>41±3.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65±1.8</td>
<td>68±2.5</td>
</tr>
<tr>
<td>Male:Female</td>
<td>17:8</td>
<td>11:14</td>
</tr>
<tr>
<td>Heart rate before reversal (beat min⁻¹)</td>
<td>74±3.1</td>
<td>71±2.5</td>
</tr>
</tbody>
</table>

Again recorded at 20 and 30 min. Oropharyngeal secretions were assessed before extubation and graded arbitrarily as "acceptable" or "excessive". Extubation was carried out when neuromuscular blockade was antagonized adequately (TOF ratio of 0.7 or more) and spontaneous ventilation had resumed.

Edrophonium was administered, in a dose of 0.5 mg kg⁻¹ in a mixture with either atropine 10 or 20 µg kg⁻¹ or glycopyrrolate 5 or 10 µg kg⁻¹, as soon as surgery had finished, but not before at least one contraction in response to TOF stimulation was present. The anticholinergic components were administered in a double-blind manner. Any patient whose neuromuscular blockade was not antagonized adequately by this dose of edrophonium received further doses, but was excluded from the study. An additional dose of the same anticholinergic agent (atropine 0.5 mg or glycopyrrolate 0.25 mg) was administered if the heart rate decreased to less than 50 beat min⁻¹. Such patients were not excluded from the study.

The ECG were examined in detail for changes in heart rate and rhythm. The heart rate changes in each group were analysed by a paired t test. The incidence of arrhythmia and the quality of secretions was analysed using Fisher's Exact test.

RESULTS

There were 25 patients in each of the four groups. They were comparable with respect to their physical characteristics and heart rate before antagonism of the neuromuscular blockade (table I). The changes in heart rate after administration of the test mixtures are shown in figure 1. The administration of atropine produced an immediate, dose-related and significant (P from < 0.001 to < 0.05) increase in heart rate, except at 1 min after 10 µg kg⁻¹, when the increase was minimal (5 beat min⁻¹). Mean heart rate increased to a peak of 83 beat min⁻¹ at 2 min following the 10-µg kg⁻¹ dose and to 89 beat min⁻¹ at 1 min following the 20-µg kg⁻¹ dose of atropine (P < 0.025 and P < 0.001, respectively). Glycopyrrolate 5 µg kg⁻¹ was associated with an initial decrease in heart rate from a mean of 70 to 64 beat min⁻¹ at 1 min after 20 µg kg⁻¹ dose of atropine (P < 0.025 and P < 0.001, respectively). Glycopyrrolate 5 µg kg⁻¹ was associated with an initial decrease in heart rate from a mean of 70 to 64 beat min⁻¹ (P < 0.005). Subsequently the heart rate increased, reaching a peak of 84 beat min⁻¹ at 1 min, and the increases were significant from 5 min onwards (P from < 0.001 to < 0.005). The higher dose of glycopyrrolate produced a significant (P < 0.001) increase in heart rate from 2 min onwards, reaching a peak of 100 beat min⁻¹ at 10 min.

Two patients receiving glycopyrrolate 5 µg kg⁻¹ required additional anticholinergic to correct a decrease in heart rate to less than 50 beat min⁻¹ occurring in both 2 min after the administration of the test drugs. The heart rates in all other patients remained above 50 beat min⁻¹, even with the lower doses of the anticholinergic drugs.
Arrhythmias were observed in 21 patients. The principal arrhythmia was junctional rhythm which was observed in 15 patients. The distribution amongst the various groups is given in table II. There was no difference in the overall incidence of arrhythmia amongst the groups; the arrhythmias resolved spontaneously without any treatment.

The changes in systolic arterial pressure were minimal: there were significant increases just before and following extubation.

The assessment of oropharyngeal secretions is depicted in figure 2. It is obvious that even the lowest doses of the anticholinergic drugs were associated with acceptable control of secretions in approximately 90% of patients. No significant differences were observed between the groups.

**DISCUSSION**

Atropine and glycopyrrolate differ in their influence on heart rate when used with edrophonium. Whereas even the lower dose of the former produces an immediate increase, the lower dose of the latter is associated with a small decrease initially. The reason for this is probably the slower time to peak effect of glycopyrrolate compared with that of atropine (Mirakhur, Jones and Dundee, 1981), and the comparatively rapid onset of the effect of edrophonium (Bevan, 1979; Cronnelly, Morris and Miller, 1982).

Although the initial decrease in heart rate of 6 beat min⁻¹ observed following glycopyrrolate 5 µg kg⁻¹ may not appear clinically important, the requirement for additional glycopyrrolate in two patients in this group as a result of a decrease in heart rate to below 50 beat min⁻¹ perhaps points to the inadequacy of this dose. Azar and colleagues (1983) also demonstrated that glycopyrrolate 0.5 mg (approximately 7.7 µg kg⁻¹) was inadequate when used with edrophonium 0.5 mg kg⁻¹. On the other hand, a 10-µg kg⁻¹ dose was associated with excessive tachycardia. Atropine 10 µg kg⁻¹ was associated with more stable heart rates which were similar to those produced by glycopyrrolate 5 µg kg⁻¹ after 4 min, but without the initial decrease in heart rate. The higher dose of atropine was also associated with unnecessarily high heart rates, but not of the same magnitude as that observed with the higher dose of glycopyrrolate.

The adequacy of the lower dose of atropine with edrophonium as the anticholinergic agent was shown also by Cronnelly, Morris and Miller (1982). These authors reported that atropine, even in a dose of 7 µg kg⁻¹, was adequate with doses of edrophonium approximately the same as those used in the present study.

It has been suggested on theoretical grounds, and without any measurement of heart rate, that atropine be administered before edrophonium (Bevan, 1979; Baird, Bowman and Kerr, 1982). This, however, appears to be unnecessary, not only from the results of the present study, but also from the studies of Cronnelly, Morris and Miller (1982) and Azar and co-workers (1983). Our data would also suggest that the onset of action of atropine is perhaps similar, if not faster, than that

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**Table II. Incidence (number of patients) and type of arrhythmia observed**

<table>
<thead>
<tr>
<th></th>
<th>Atropine 10 µg kg⁻¹</th>
<th>Atropine 20 µg kg⁻¹</th>
<th>Glycopyrrolate 5 µg kg⁻¹</th>
<th>Glycopyrrolate 10 µg kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular ectopic beats</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prolongation of P-R interval</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Fig. 2. Secretions following reversal. Cross-hatched columns = acceptable; open columns = excessive.**
of edrophonium, since both doses of atropine produced an immediate increase in heart rate.

The overall picture from the present study suggests that edrophonium exerts weak muscarinic effects, since even the lower dose of atropine was sufficient to prevent bradycardia. This is supported further by the acceptable control of oropharyngeal secretions achieved using the lower doses of the anticholinergic drugs.

In conclusion, the doses of anticholinergic agents can be decreased safely when used in association with edrophonium, in comparison with those required with neostigmine. Atropine in a dose of 10 μg kg⁻¹ appears to be the agent of choice with edrophonium 0.5 mg kg⁻¹ when given to antagonize neuromuscular blockade. Whereas glycopyrrolate 5 μg kg⁻¹ does not provide complete protection against the edrophonium-induced decreases in heart rate, the higher dose is associated with excessive tachycardia.

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REFERENCES