GLYCOPYRROLATE AS A PREMEDICANT: COMPARISON WITH ATROPINE

T. D. MCCUBBIN, J. H. BROWN, K. M. S. DEWAR, C. J. JONES AND A. A. SPENCE

SUMMARY

A double-blind comparison of glycopyrrolate with atropine as the anticholinergic component of premedication was made in 200 patients undergoing minor or intermediate surgical procedures. Glycopyrrolate was associated with a smaller increase in heart rate, but there was no difference between the drugs in respect of cardiac arrhythmia, change in arterial pressure, control of secretions in the upper respiratory tract, frequency of nausea and vomiting after operation or subjective well-being of the patients.

In 1960, glycopyrrolate, a quaternary ammonium compound, was introduced as a potent long-acting anticholinergic agent which apparently offered a smaller frequency of side-effects such as dryness of the mouth, blurring of vision and excessive tachycardia seen with atropine.

More recently, several studies of the relative effects of glycopyrrolate and atropine combined with neostigmine and given i.v. for antagonism of neuromuscular blockade concluded that the glycopyrrolate-neostigmine combination produced a more stable heart rate with a reduced frequency of tachycardia and arrhythmia (Ramamurthy, Ylagan and Winnie, 1971; Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). Being a quaternary ammonium compound, glycopyrrolate crosses the blood–brain barrier to a minimal degree compared with atropine, a tertiary amine (Proakis and Harris, 1978). Therefore, glycopyrrolate should exert none of the central effects that occasionally occur with atropine. Wyant and Kao (1974) found that glycopyrrolate was a more effective antisialogogue than atropine. Glycopyrrolate is at present freely available in the U.S.A. and is being widely promoted on the basis of the attributes mentioned above.

We have undertaken a double-blind comparison of atropine with glycopyrrolate as the anticholinergic components of premedication, to determine if the latter drug appeared to have any advantages over atropine.

PATIENTS AND METHODS

Two hundred healthy patients were studied; none was receiving concurrent drug therapy. The age and sex distribution and types of operation are shown in table I. Premedication consisted of morphine 10 mg and either atropine 0.6 mg or glycopyrrrolate 0.2 mg (randomly allocated) administered i.m. approximately 1 h before operation. Just before the injection, the heart rate and arterial pressure were recorded (resting values).

Before induction of anaesthesia, the patients were asked:

Do you feel drowsy?
How do you feel otherwise?
How does your mouth feel—normal, dry or uncomfortably dry?

Anaesthesia was induced with thiopentone 2.5% sufficient to abolish the eyelash reflex, and tracheal intubation was facilitated by suxamethonium 50 mg. Anaesthesia was maintained with 66% nitrous oxide in oxygen supplemented by halothane as necessary using a Magill breathing system. After recovery from suxamethonium the patients breathed spontaneously. E.c.g. was monitored throughout (Memory Monitor, SEM 432, S.E. Labs) and heart rate, arterial systolic pressure (oscillotonometer), and the presence of arrhythmia were recorded before induction, before and following incision, and at 15-min intervals thereafter. At the end of the operation, the oropharynx was aspirated before removal of the tracheal tube and the aspirate volume was judged by the anaesthetist to be "acceptable" or "excessive". Following recovery from anaesthesia, the patients were questioned about the state of the mouth on wakening and about any experience of nausea or vomiting. Patients anaesthetized in the morning were interviewed in the evening of the same day. Patients anaesthetized in the afternoon were interviewed in the morning of the following day. All the anaesthetics were given by a Consultant or Senior Registrar (one of the authors).

Patients were selected from each group and matched for age, sex, type of operation and premedication–induction interval; 67 pairs (134 patients) fulfilled these criteria.

The data were analysed using Chi square test and Student's $t$ test for analysis of paired data.

**RESULTS**

**Assessment before induction**

Forty per cent of patients in the atropine group and 38% in the glycopyrrolate group felt drowsy; 15% in the atropine group and 16% in the glycopyrrolate group commented spontaneously about mouth dryness; the responses to direct questioning regarding mouth dryness are in table II. There were no significant differences between the drugs in respect of any of these criteria.

**Observations during operation**

**Heart rate.** Figure 1 shows the percentage of patients in whom there was an increase in heart rate. The only significant difference between the drug groups was in the period before induction, when a significantly higher proportion of patients in the atropine group exhibited an increase in heart rate of $\geq 10\% \ (P<0.05)$, $\geq 20\% \ (P<0.01)$ and $\geq 30\% \ (P<0.005)$.

Table III (matched comparison) shows the mean percentage increase in heart rate attributable to atropine or glycopyrrolate. The only significant difference between the groups was at the period before induction.

**TABLE III. Analysis of matched pairs. Mean % increase in heart rate attributable to atropine or glycopyrrolate**

<table>
<thead>
<tr>
<th></th>
<th>Before induction</th>
<th>Before incision</th>
<th>After incision (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean diff.</strong></td>
<td>10.15</td>
<td>5.35</td>
<td>4.42</td>
</tr>
<tr>
<td><strong>t</strong></td>
<td>3.25</td>
<td>1.30</td>
<td>1.13</td>
</tr>
<tr>
<td><strong>Deg. freedom</strong></td>
<td>66</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.005</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Arrhythmia was observed in 10 patients in the atropine group and in 11 in the glycopyrrolate group; eight and six respectively had unifocal or multifocal ventricular ectopic beats or bigeminy. In the glycopyrrolate group, four others developed a heart rate less than 50 beat min$^{-1}$ and one patient had a "wandering pacemaker". In the atropine group, one patient had supraventricular tachycardia and another developed multifocal extrasystoles proceeding to ventricular tachycardia; anaesthesia and operation were discontinued but the patient made an uneventful recovery. No obvious predisposing factors could be found for these arrhythmias. A few patients exhibited decreases in heart rate, but there was no significant difference between the groups.

**Arterial pressure.** Figure 2 shows the percentage of patients exhibiting increases in arterial systolic pressure equal to or greater than 20 mm Hg and 40 mm Hg compared with the resting value. The majority of patients exhibited a progressive decrease in pressure and there was no significant difference between the two groups (fig. 3).

**Secretions.** Acceptable control of oropharyngeal secretions was achieved in 94% of patients in the

**TABLE II. Assessment of dryness of mouth (A) before induction and (B) after operation**

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Glycopyrrolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomfortably dry</td>
<td>A 14</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>B 46</td>
<td>58</td>
</tr>
<tr>
<td>Dry</td>
<td>A 79</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>B 39</td>
<td>33</td>
</tr>
<tr>
<td>Normal</td>
<td>A 7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>B 15</td>
<td>9</td>
</tr>
</tbody>
</table>
GLYCOPRYROLATE AND ATROPINE IN PREMEDICATION

Fig. 1. Percentage of patients exhibiting increases in heart rate ≥10% (upper trace), ≥20% (middle trace) and ≥30% (lower trace), compared with resting value at the times (min) indicated. The number of patients for whom a measurement was available is given in brackets. Pre Ind = before induction; Inc = incision.

Fig. 2. Percentage of patients exhibiting increases in systolic arterial pressure ≥20 mm Hg (upper trace) and ≥40 mm Hg (lower trace), compared with resting value at the times indicated.

Assessment after operation. Thirty-eight per cent of patients in the atropine group and 39% in the glycopyrrolate group experienced nausea or vomiting, or both, in the period after operation. The patients' comments as to the state of the mouth on wakening are in table II. Both before and after operation, the majority of patients in both groups complained of mouth dryness, with more in the glycopyrrolate group stating that this was uncomfortable. However, the difference between the groups was not statistically significant.

DISCUSSION

We found that only in the period before induction of anaesthesia did significantly fewer patients in the glycopyrrolate group exhibit increases in heart rate compared with the atropine group. However, that is perhaps the most valid period for direct comparison of the drugs, as subsequent measurements were obviously influenced by a variety of factors associated with anaesthesia and operation. This conclusion is based on analysis of group means and is supported further by the analysis of matched pairs, the latter
device being used to reduce the influence of age, sex
and operation. A comparison of percentage changes
in heart rate between the groups at subsequent periods
of measurement failed to reveal any significant
differences, although in general a smaller proportion
of patients receiving glycopyrrolate showed increases
in heart rate during each period of observation
compared with those receiving atropine.

Various authors have described improved cardio-
vascular stability with a reduced frequency of
tachycardia and arrhythmia when glycopyrrolate was
substituted for atropine in combination with neo-
stigmine to antagonize neuromuscular blockade
(Ramamurthy, Ylagan and Winnie, 1971; Klingen-
maier et al., 1972; Ramamurthy, Shaker and Winnie,
1972; Oduro, 1975; Mirakhur, Dundee and Clarke,
1977).

The patients in this study were healthy, under-
going relatively simple surgical procedures, and an
increased heart rate may be considered acceptable.
However, glycopyrrolate may offer advantages in the
management of patients with cardiovascular disease
or hyperthyroidism, or if a technique for induced
hypotension is used. In this study, the majority of
arrhythmias were benign and required no treatment;
indeed, cardiac arrhythmia is not infrequent with the
technique of anaesthesia employed in this investiga-
tion (Katz and Bigger, 1970). Mirakhur and others
(1978b) noted a reduced frequency of arrhythmia
with the use of glycopyrrolate when used as a
premedicant, but our findings fail to confirm this.

It has been suggested (Ramamurthy, Ylagan and
Winnie, 1971; Ramamurthy, Shaker and Winnie,
1972) that atropine, a tertiary amine, can cross the
blood–brain barrier and may cause c.n.s. excitation;
glycopyrrolate, a quaternary ammonium compound,
cannot readily cross the blood–brain barrier. However,
we detected no difference in drowsiness before
operation between the two groups.

There was no difference between the groups in the
occurrence of nausea and vomiting after operation;
the use of morphine in sedation before surgery may
account for the high overall frequency of post-
operative nausea and vomiting which we noted
(Riding, 1960). Dr Riding also demonstrated the
antiemetic properties of atropine. It has been
observed that the awake patient who has received
glycopyrrolate complains less of mouth dryness than
does the patient who has received atropine (Rama-
murthy, Ylagan and Winnie, 1971). However, our
study failed to confirm this either before or after
operation.

The routine use of anticholinergic drugs before
operation is controversial, but in a recent survey,
Mirakhur and others (1978a) pointed out that more
than 60% of anaesthetists in the U.K. employ such a
drug, and therefore the majority of patients under-
going general anaesthesia receive an anticholinergic
agent. We can conclude from this study that glyco-
pyrrolate is an acceptable alternative to atropine,
although, apart from considerations of heart rate, it
does not have any dramatic advantage over atropine.

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REFERENCES
mias during anaesthesia and operation. Anesthesiology, 33,
193.
Klingenmaier, C. H., Bullard, R., Thompson, D., and
Watson, R. (1972). Reversal of neuromuscular blockade
with a mixture of neostigmine and glycopyrrolate.
Mirakhur, R. K., Clarke, R. S. J., Dundee, J. W., and
McDonald, J. R. (1978a). Anticholinergic drugs in
anaesthesia: a survey of their present position. Anaesthesia,
33, 133.
Elliott, J., and Dundee, J. W. (1978b). Atropine-
glycopyrromium premedication. A comparison of the
effects on cardiac rate and rhythm during induction of
anaesthesia. Anaesthesia, 33, 906.


**LE GLYCOPYRROLATE EN TANT QUE PREMEDICATION: COMPARAISON AVEC L'ATROPINE**

**RESUME**

On a fait sur 200 malades devant subir des interventions chirurgicales mineures ou intermédiaires des comparaisons à double inconnue du glycopyrrolate et de l'atropine en tant que composant anticholinergique de la prémédication. Le glycopyrrolate a été associé à une plus petite augmentation de la fréquence cardiaque, mais il n'y a eu aucune différence entre les médicaments en ce qui concerne l'arythmie cardiaque, les variations dans la pression artérielle, le contrôle des sécrétions dans les voies respiratoires supérieures, la fréquence des nausées et des vomissements après l'opération ou le bien-être subjectif des patients.

**GLYCOPYRRONIUM-BROMID FÜR DIE VORBEHANDLUNG: VERGLEICH MIT ATROPIN**

**ZUSAMMENFASSUNG**


**GLICOPIRROLATO COMO SUSTANCIA DE PREMEDICACIÓN: COMPARACION CON ATROPINA**

**SUMARIO**

Se llevó a cabo en 200 pacientes sometidos a operaciones quirúrgicas menores o intermedias una comparación doble ciega de glicopirrolato con atropina, como componente anti- colinérgico de premedicación. Se comprobó que el glicopirrolato se acompañaba de un pequeño aumento del ritmo cardíaco, pero que no había diferencia entre las drogas con respecto a arritmia cardíaca, cambios en la presión arterial, control de secreciones en vías respiratorias altas, frecuencia de las náuseas y vómitos después de la operación o bienestar subjectivo de los pacientes.