COMPARISON OF I.V. GLYCOPRYRROLATE AND ATROPINE IN THE PREVENTION OF BRADYCARDIA AND ARRHYTHMIAS FOLLOWING REPEATED DOSES OF SUXAMETHONIUM IN CHILDREN

D. W. GREEN, A. S. E. BRISTOW AND M. FISHER

SUMMARY
The effectiveness of administration of glycopyrrolate 5 and 10 μg kg⁻¹ and atropine 10 and 20 μg kg⁻¹ i.v. immediately before the induction of anaesthesia, to prevent arrhythmia and bradycardia following repeated doses of suxamethonium in children, was studied. A control group was included for comparison with the lower dose range of glycopyrrolate and atropine. A frequency of bradycardia of 50% was noted in the control group, but this was not significantly different from the frequency with the active drugs. Bradycardia (defined as a decrease in heart rate to less than 50 beat min⁻¹) was prevented when the larger dose of either active drug was used. It is recommended that either glycopyrrolate 10 μg kg⁻¹ or atropine 20 μg kg⁻¹ i.v. should immediately precede induction of anaesthesia, in children, if the repeated administration of suxamethonium is anticipated.

Bradycardia may follow repeated i.v. injections of suxamethonium (Savarese, 1981). The mechanism appears to involve stimulation of cardiac parasympathetic postsynaptic receptors in a fashion analogous to that of acetylcholine, and this may lead to sinus arrest (McLeskey et al., 1978). Although Martin (1958) reported that this effect could be decreased by the administration of atropine as a premedicant, it is disputed whether premedication with atropine or glycopyrrolate i.m. can prevent bradycardia following repeated doses of suxamethonium (Cozanitis et al., 1982). Indeed, the efficacy of atropine i.v. in preventing the bradycardia caused by repeated doses of suxamethonium has been questioned (Cozanitis, Dundee and Khan, 1980).

Suxamethonium-induced bradycardia is more likely in sympathotonic individuals, such as children (Craythorne, Turndoff and Dripps, 1960; Leigh, McCoy and Belton, 1957) and although glycopyrrolate i.v. has been compared with atropine in children who required suxamethonium to facilitate intubation (Lavis, Lunn and Rosen, 1980), no controlled trial has been carried out to compare these two drugs following the repeated administration of suxamethonium.

PATIENTS AND METHODS
The trial was divided into two stages:

Stage 1
Twenty-six children younger than 14 yr, about to undergo oesophagoscopy, duodenoscopy and injection of oesophageal varices were weighed, and premedicated with diazepam 0.2 mg kg⁻¹ orally 2 h before surgery. On arrival in the anaesthetic room, each child was connected to a portable electrocardiogram (ECG) with ratemeter and printout, and control measurements obtained.

The drug solutions were glycopyrrolate 0.2 μg ml⁻¹, atropine 0.4 μg ml⁻¹ and normal saline. These were administered i.v. on a double-blind basis following randomization in a volume of 0.025 ml kg⁻¹, equivalent to glycopyrrolate 5 μg kg⁻¹, atropine 10 μg kg⁻¹ or saline (control). The effect on heart rate was observed for 3 min, and was followed by the induction of anaesthesia with thiopentone 5 mg kg⁻¹. Suxamethonium 2 mg kg⁻¹ was given to facilitate tracheal intubation. In a few patients who received halothane for the induction of anaesthesia, the test drug was administered at least 1 min before the injection of suxamethonium. Anaesthesia was maintained with nitrous oxide and 0.5% halothane in oxygen with controlled ventilation. Arterial pressure was measured automatically (Dinamap, Critikon Inc. Tampa, Florida, U.S.A.) at 1-min intervals throughout the procedure.

Repeated doses of suxamethonium 0.5 mg kg⁻¹ were given on the first return of muscle twitch as monitored by a peripheral nerve stimulator (Mini-stim, Professional Instruments Co., Houston, Texas, U.S.A.) using the ulnar nerve at the wrist. The heart rate was recorded at 1-min intervals during the procedure, particular note being made of any
bradycardia following the suxamethonium. If the rate decreased to less than 50 beat min⁻¹, the code was broken and appropriate treatment instituted. All arrhythmias were recorded.

Stage 2

The control group was eliminated following Stage 1, and the volume of the active preparations was doubled. The patients thus received 0.05 ml kg⁻¹ of drug, equivalent to glycopyrrolate 10 μg kg⁻¹ or atropine 20 μg kg⁻¹; otherwise, the test procedure was as outlined above.

RESULTS

Stage 1

Of the 26 patients, 10 received glycopyrrolate, 10 atropine and six saline (control). Some details of the patients studied are shown in table I. There were no statistically significant differences between the groups.

The frequency of arrhythmia and bradycardia observed in Stage 1 is shown in table II. There was no statistically significant difference in the occurrence of bradycardia between the two "treated" groups and the control group (Fisher's exact test).

Stage 2

Twenty-three patients were studied, of whom 14 received atropine and nine glycopyrrolate. Details of the patients in Stage 2 are shown in table III. There were no statistically significant differences between the groups.

The results in table IV show that the frequency of arrhythmias and bradycardia was decreased substantially by the larger dose of the two anticholinergic drugs. Only one episode of arrhythmia was noted (following atropine), and bradycardia did not occur in any patient.

The effect of glycopyrrolate and atropine on increasing the heart rate before the administration of the first dose of suxamethonium was also calculated from the results during both stages (table V). There were no statistically significant differences between the two drugs when compared at either dose range. Thus, the larger dose of either drug did not cause a significantly greater increase in heart rate than the smaller dose. At both doses, atropine caused a significant increase in heart rate over the control group, whereas with glycopyrrolate this was only so with the higher dose.

DISCUSSION

The emphasis in this study was to prevent significant bradycardia-arrhythmias in all patients following the repeated administration of suxamethonium. It should be noted that some studies were carried out before surgery (Cozanitis et al., 1982). Thus, in the present study, less emphasis was placed on the difference in the decreases in heart rate with repeated doses of suxamethonium following the active drugs, than on the actual prevention of bradycardia.

The use of the control group in Stage 1 may be considered unethical by some (Cozanitis, Dundee and Khan, 1980). However, the results of Cozanitis and colleagues (1982) suggested that the smaller dose range given i.m. was no more effective than saline control. Their control group was added later and was not randomized. The high frequency of bradycardia in the control group in this study sug-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Glycopyrrolate</th>
<th>Atropine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Yes</td>
<td>No</td>
<td>n</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Atropine</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Glycopyrrolate</th>
<th>Atropine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Yes</td>
<td>No</td>
<td>n</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Atropine</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
suggests that all patients should receive anticholinergic drugs i.v. before the repeated administration of suxamethonium. When the smaller dose of anticholinergic was used, it was noted that a modest slowing of the heart rate following, say, the third dose of suxamethonium, would often lead to a more severe decrease after subsequent doses. There was no evidence of tachyphylaxis to repeated doses as has been reported in some studies (Graf, Strom and Wahlin, 1963).

One might ask why a non-depolarizing agent was not used. In this study of 49 patients, 10 received two doses of suxamethonium or fewer. Thus, from clinical experience, it was considered that 20% of patients would have a duration of operation of less than 10 min, too short for easy reversal from non-depolarizing blockade. Initial experience with atracurium does not suggest this agent to be any better in this respect.

The use of pre-suxamethonium blockade with a small dose (less than one-quarter of the full relaxing dose) of a non-depolarizing neuromuscular blocking drug is said to prevent bradycardia following a second dose of suxamethonium (Mathias, Evans-Prosser and Churchill-Davison, 1970), although the efficacy of this technique has been disputed (Wisborg, Christensen and Viby-Mogensen, 1977). The latter group contend that thiopentone, as opposed to halothane, may provide some protection against bradycardia during halothane anaesthesia (Viby-Mogensen, Wisborg and Sorensen, 1980), but evidence for this was not found in our study.

Preoperative medication with atropine has been advocated by Martin (1958). However, the study of Viby-Mogensen and colleagues (1976) does not support this view. They suggest that the administration of atropine before operation does not protect against serious brady-arrhythmias following a second dose of suxamethonium, unless doses of atropine are used which cause tachycardia of considerable degree. This did not happen with the doses used i.v. in the present study; in this respect the findings are in agreement with those of Cozanitis, Dundee and Khan (1980).

This study has shown that bradycardia following repeated doses of suxamethonium in children may be prevented by an adequate dose of anticholinergic drugs i.v. immediately before the induction of anaesthesia. This dose must be about 10 μg kg⁻¹ of glycopyrrolate or 20 μg kg⁻¹ of atropine. Both drugs were equally effective, and increasing the dose to this level did not cause excessive tachycardia. Since this study was completed, a further 50 patients have been studied using glycopyrrolate 10 μg kg⁻¹ in the manner described. No instance of bradycardia has been observed. Unfortunately, although
glycopyrrolate i.v. is twice as potent as atropine on a weight per kilogram basis in anaesthetized patients (Mirakhur, Jones and Dundee, 1980), the commercial preparation of atropine in the U.K. is three times the concentration (unlike the strength used in this study). This makes dose calculation more difficult with atropine, and theoretical considerations also suggest that the quaternary ammonium compound, glycopyrrolate, may be preferable because of lack of CNS effects. Hunsley, Bush and Jones (1982) noted central effects in children following administration of smaller doses of atropine than the maximum dose used in this study. However, in this study, no important side-effects were noted with either drug in the period after operation.

ACKNOWLEDGEMENTS

We would like to thank A. H. Robins Co. Ltd, Horsham, West Sussex, for the double-blind ampoules of atropine and glycopyrrolate. Mrs V. L. Pooley typed the manuscript.

REFERENCES


COUPEAU DUT GLYCOPYRROLATE I.V. ET DE L'ATROPINE DANS LA PREVENTION DE LA BRADYCARDIE ET DES TROUBLES DU RYTHME INDUCTS PAR DES DOSES REPETEES DE SUXAMETHONIUM CHEZ L'ENFANT

RESUME

Nous avons étudié l'efficacité de l'administration i.v. de 5-10 μg kg⁻¹ de glycopyrrolate ou de 10-20 μg kg⁻¹ d'atropine immédiatement avant l'induction de l'anesthésie, dans la prévention des troubles du rythme et de la bradycardie induits par des doses répétées du suxamethonium chez l'enfant. Un groupe contrôle a été inclus pour comparaison avec les plus faibles doses de glycopyrrolate et d'atropine. Dans le groupe contrôle, une fréquence de 50% de bradycardies a été notée mais ceci n'était pas significativement différent de la fréquence retrouvée avec les agents actifs. La bradycardie (définie comme une diminution de la fréquence cardiaque au-dessous de 5 ou 6 b.p.m.) était prévenue par l'utilisation des posologies les plus élevées des deux agents. Nous préconisons l'injection i.v. de 10 μg kg⁻¹ de glycopyrrolate ou de 20 μg kg⁻¹ d'atropine immédiatement avant l'induction de l'anesthésie chez l'enfant lorsqu'on prévoit que des injections répétées de suxamethonium seront nécessaires.

Se llevó a cabo el estudio de la eficacia de la administración de 5 y 10 µg kg⁻¹ de glicopirrolato y de 10 y 20 µg kg⁻¹ de atropina i.v. inmediatamente antes de la inducción de anestesia con el objeto de prevenir las arritmias y la bradicardia a raíz de dosis repetidas de suxametoino en niños. Se incluyó a un grupo de control con miras a compararlo con la gama más baja de dosis de glicopirrolato y de atropina. Se observó una frecuencia del 50% de bradicardia en el grupo de control, pero no difería de manera significativa de la frecuencia observada con las substancias activas. Se previno la bradicardia (definida como un descenso del ritmo cardíaco a menos de 50 latidos min⁻¹) cuando se usó la dosis mayor de cualquiera de las substancias activas. Se recomienda que se administre ya sea 10 µg kg⁻¹ de glicopirrolato ya sea 20 µg kg⁻¹ de atropina i.v. inmediatamente antes de la inducción de la anestesia en niños si se contempla la administración repetida de suxameto.