CARDIOVASCULAR EFFECTS OF ALCURONIUM IN MAN

By
B. R. KENNEDY and G. R. KELMAN

SUMMARY

We have investigated the effects of alcuronium (0.15 mg/kg body weight) on heart rate, stroke volume, cardiac output, mean arterial blood pressure and total peripheral resistance in 22 artificially ventilated patients anaesthetized with 60 per cent nitrous oxide in oxygen, plus either tubocurarine (25–35 mg, according to body weight) and 0.2 per cent methoxyflurane—series I—or phenoperidine (1 mg/15 kg body weight)—series II. End-tidal Pco₂ was maintained constant. The most striking effect was a significant increase of heart rate in the series II patients, accompanied by a significant fall of cardiac output and of stroke volume. There was no significant change of mean arterial pressure in either series of patients; therefore the fall of cardiac output was accompanied by a compensatory increase of total peripheral resistance.

Alcuronium, a synthetic derivative of the alkaloid C-toxiferine-I, was introduced into anaesthetic practice by Hügin and Kissling in 1961. Although this drug is now a commonly used muscle relaxant, its effects on the human cardiovascular system have not been fully explored. The object of the present study was to assess the cardiovascular effects of alcuronium in anaesthetized humans, while avoiding, as far as possible, cardiovascular disturbances from other causes. The dose used (0.15 mg/kg body weight) was chosen to be in keeping with current clinical practice.

METHOD

The 22 subjects investigated were adult inpatients undergoing routine surgery. All were in good health apart from their presenting surgical complaint. The age, weight, and sex of each patient, together with the dose of premedicant and induction agent used are shown in table I. All patients had given consent to the performance of the investigation.

One of two anaesthetic techniques was used. In both cases anaesthesia was induced with intravenous thiopentone (200–400 mg). The patients in series I (12 patients) were then paralyzed with tubocurarine (25–35 mg according to body weight) and artificially ventilated with 60 per cent nitrous oxide in oxygen via a cuffed endotracheal tube. Methoxyflurane was added to the inspired gas mixture in a concentration of 0.2 per cent from a Pentec vaporizer. Patients in series II (10 patients) were intubated after administration of suxamethonium (50–60 mg); respiratory depression sufficient to permit controlled ventilation with a mixture of 60 per cent nitrous oxide in oxygen was then produced with phenoperidine (1 mg/15 kg body weight).

Intermittent positive pressure ventilation was performed throughout the period of investigation with a Manley ventilator and a non-rebreathing circuit. End-tidal Pco₂ was monitored continuously with an infra-red carbon dioxide analyzer (URAS 3, Hartmann and Braun) and the ventilatory minute volume adjusted to maintain the end-expiratory Pco₂ at 30 ± 2 mm Hg.

Twenty minutes after induction of anaesthesia, all the patients in each series were given an intravenous injection of alcuronium (0.15 mg/kg body weight). Control measurements of heart rate, arterial blood pressure and cardiac output were made immediately before, at 17 and 19 minutes after induction. These measurements were repeated at 2, 5 and 10 minutes after the injection of alcuronium (groups 2 and 4, table I) or at an equivalent time in the control patients who received no alcuronium (groups 1 and 3, table I). Measurements were completed before the start of surgery.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Wt (kg)</th>
<th>Premedication P/H (mg)</th>
<th>Thiopentone (mg/kg)</th>
<th>Tubocurarine (mg)</th>
<th>Suxamethonium (mg)</th>
<th>Phenoperidine (mg)</th>
<th>Alcuronium (mg/kg)</th>
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<td>M</td>
<td>62</td>
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<td>M</td>
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<td>10/0.4</td>
<td>5.4</td>
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<td>M</td>
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<td>50</td>
<td>4.0</td>
<td>0.15</td>
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<tr>
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<td>—</td>
<td>50</td>
<td>5.0</td>
<td>0.15</td>
</tr>
</tbody>
</table>

P = papaveretum  
H = hyoscine
Heart rate was measured from an e.c.g. tracing. This tracing was also scrutinized for the occurrence of arrhythmias. Arterial blood pressure was measured by an oscillometer to the nearest 5 mm Hg. Cardiac output was estimated by the dye dilution technique using indocyanine green and a Waters XE302 photoelectric earpiece and associated electronic equipment. Accurate estimation of changes of cardiac output is possible with the earpiece technique (Gabe, Tuckman and Shillingford, 1962), but absolute values cannot be obtained unless samples of arterial blood are withdrawn immediately after inscription of the dye curve. Arterial puncture, however, would defeat the object of using an earpiece. For this reason all output measurements in the present study are expressed as a percentage of the control values obtained immediately before an injection of alcuronium.

RESULTS
The initial values of mean arterial blood pressure (diastolic plus one-third pulse pressure) and mean heart rate are given in table II.

The percentage change of heart rate, cardiac output, stroke volume, blood pressure and total peripheral resistance in the various groups of patients, 2, 5 and 10 minutes after administration

<table>
<thead>
<tr>
<th>Table II</th>
<th>Actual mean arterial pressure and mean heart rate values in patients before the injection of alcuronium (or no alcuronium in the control patients).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>1</td>
<td>75</td>
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<tr>
<td>2</td>
<td>75</td>
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<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
</tr>
</tbody>
</table>

Series I
| Group     | Mean arterial pressure (mm Hg) | Mean heart rate (beats/min) |
| 6         | 85                               | 53                          |
| 7         | 85                               | 100                         |
| 8         | 60                               | 71                          |
| 9         | 80                               | 58                          |
| 10        | 75                               | 60                          |
| 11        | 80                               | 47                          |
| 12        | 85                               | 77                          |

Series II
| Group     | Mean arterial pressure (mm Hg) | Mean heart rate (beats/min) |
| 13        | 90                               | 72                          |
| 14        | 85                               | 56                          |
| 15        | 55                               | 39                          |
| 16        | 85                               | 70                          |
| 17        | 70                               | 43                          |

Mean ± SEM 74.8 ± 2.3 62.1 ± 3.0

Table III
Circulatory changes in each series of patients. Those in the control groups, 1 and 3, received no alcuronium while those in groups 2 and 4 were given alcuronium 0.15 mg/kg.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Circulatory changes in each series of patients. Those in the control groups, 1 and 3, received no alcuronium while those in groups 2 and 4 were given alcuronium 0.15 mg/kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series I (rubocurarine + methoxyflurane)</td>
<td>Group 1 (control) n = 5</td>
</tr>
<tr>
<td>Heart rate</td>
<td>2 min 98.5 ± 1.2 n.s.</td>
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<tr>
<td></td>
<td>5 min 95.3 ± 0.9 **</td>
</tr>
<tr>
<td></td>
<td>10 min 92.8 ± 1.7*</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>2 min 94.4 ± 1.8*</td>
</tr>
<tr>
<td></td>
<td>5 min 89.5 ± 2.4*</td>
</tr>
<tr>
<td></td>
<td>10 min 81.9 ± 3.2**</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>2 min 95.7 ± 2.7 n.s.</td>
</tr>
<tr>
<td></td>
<td>5 min 94.0 ± 3.0 n.s.</td>
</tr>
<tr>
<td></td>
<td>10 min 86.5 ± 4.2*</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td>2 min 99.2 ± 1.4 n.s.</td>
</tr>
<tr>
<td></td>
<td>5 min 99.1 ± 1.4 n.s.</td>
</tr>
<tr>
<td></td>
<td>10 min 99.4 ± 1.3 n.s.</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>2 min 105.2 ± 3.0 n.s.</td>
</tr>
<tr>
<td></td>
<td>5 min 110.5 ± 3.4*</td>
</tr>
<tr>
<td></td>
<td>10 min 121.3 ± 4.6**</td>
</tr>
<tr>
<td>All figures per cent (mean ± SEM). * 0.01&lt;P&lt;0.05. ** P&lt;0.01. All comparisons with 100.0 per cent. n.s. = not statistically significant.</td>
<td></td>
</tr>
</tbody>
</table>
of 0.15 mg/kg alcuronium (or at equivalent times in the control patients) is given in table III, together with the statistical significance of the difference from 100 per cent (no change, which represents the condition 20 minutes after induction of anaesthesia).

In the first series (tubocurarine plus methoxyflurane) there was a progressive and statistically significant fall of heart rate in the control patients, and a slight but not statistically significant increase of rate in the patients who were given alcuronium. In both cases there was a fall of cardiac output accompanied by a similar fall of stroke volume. The fall of cardiac output was greater in the patients who did not receive alcuronium, although the difference does not quite reach statistical significance at the 0.05 level. In both groups there was a slight, and not statistically significant fall of blood pressure accompanied by an increase of calculated total peripheral resistance, which was more marked in the control patients.

In the second series (suxamethonium plus phenoperidine) there was an increase of heart rate in the patients who were given alcuronium, whereas there was no appreciable change of heart rate in the control patients. There was no significant change of cardiac output in the control patients; in the patients who had received alcuronium, however, cardiac output initially showed a significant increase, and later, a significant decrease. These changes were accompanied by parallel changes of stroke volume. There was no significant change of blood pressure and total peripheral resistance in either group of this series.

DISCUSSION
The problems involved in the study of the cardiovascular effects of muscle relaxants have been discussed previously (Kennedy and Farman, 1968). In the present investigation, an interval of 20 minutes was allowed between induction of anaesthesia and commencement of the measurements. In this way the haemodynamic effects of the induction agents were minimized, and the patients had time to reach a steady state with regard to arterial carbon dioxide tension and other physiological variables. The patients were undisturbed by surgical or other stimuli before and during the investigation. Respiratory minute volume was adjusted to maintain end-tidal carbon dioxide tension constant to prevent the alterations of cardiac output which may occur with changes of arterial carbon dioxide tension (Prys-Roberts et al., 1967, 1968). Continuous electrocardiographic monitoring throughout the study failed to demonstrate the occurrence of any arrhythmias.

The anaesthetic agents used were chosen to permit controlled ventilation with minimal circulatory upset. In the series II control group almost complete cardiovascular stability was achieved throughout the period of measurement.

The results suggest that the principal cardiovascular effect of alcuronium is to cause an increase of heart rate. In the series I (tubocurarine plus methoxyflurane) patients there was a progressive fall of heart rate in the control group. This fall did not occur in the patients who were given alcuronium. This progressive bradycardia in the control patients may be attributed to tubocurarine, which causes an initial tachycardia followed by bradycardia (Tammisto and Welling, 1969). In the series II (suxamethonium plus phenoperidine) patients there was an increase of heart rate after the administration of alcuronium. There was no appreciable reduction of heart rate in the control patients; this is in keeping with the finding of Prys-Roberts and Kelman (1967) that heart rate is not reduced by phenoperidine. We therefore believe that alcuronium causes a significant increase of heart rate, although this effect was masked by tubocurarine in the series I patients.

This finding differs from the results of in vitro studies on heart-lung preparations and isolated guineapig atria, where alcuronium causes bradycardia (Droh and Horst, 1965). In human investigations, reports of alteration of heart rate with alcuronium have been few. Stovner and Lund (1964) found that heart rate increased by up to 20 beats/min after administration of alcuronium (0.20-0.25 mg/kg); these measurements were made, however, at the time of endotracheal intubation, a procedure well known to cause tachycardia (Rollason and Hough, 1957). Tammisto and Welling (1969) found an increase of heart rate following administration of alcuronium in a dose of 0.15 mg/kg, and a greater effect with twice this dose.
Progressive reduction of stroke volume occurred in both groups in series I. The falls were of similar magnitude. We conclude that alcuronium played no part in this change since the amount of the fall was similar in both cases. Both tubocurarine (Smith and Whitcher, 1967) and methoxyflurane (Walker, Eggers and Allan, 1962) may cause such a decrease of stroke volume. No changes in stroke volume were observed in the control group in series II, but a significant reduction occurred after the administration of alcuronium. These findings seem to be best explained by the fact that the series II patients were not paralyzed. Paralysis by administration of alcuronium might be expected to cause pooling of blood in the skeletal muscles, with a consequent reduction of cardiac output and stroke volume. Indirect evidence for this hypothesis is provided by the time course of the reduction in stroke volume; muscle relaxation would not be complete for some minutes after the administration of alcuronium.

The values of cardiac output reflect the alterations of heart rate and stroke volume discussed above. In both groups of patients who received alcuronium the falls in cardiac output were less than the falls of stroke volume, presumably due to tachycardia produced by the alcuronium. Mean arterial pressure was little affected by alcuronium, a finding in keeping with the work of Tammisto and Welling (1969). Marked falls of blood pressure have been reported by other workers (Hunter, 1964; Baraka, 1967). However, these studies generally relate to larger doses than we have used.

Similar changes of total peripheral resistance were found in all patients who received alcuronium. There was an initial fall followed by an eventual rise above the value found before the administration of alcuronium. The mean arterial pressure did not change significantly throughout the period of measurement, therefore the alterations of total peripheral resistance were inversely proportional to changes of cardiac output, presumably as a result of baroreceptor reflexes. Alcuronium is not known to possess any direct action on peripheral blood vessels.

We conclude that the principal effect of alcuronium (0.15 mg/kg) on the human cardiovascular system is to cause a mild increase of heart rate. This tachycardia may compensate for peripheral pooling of blood in paralyzed skeletal muscles, thus minimizing the reduction of cardiac output.

ACKNOWLEDGEMENTS

We wish to express our thanks to Dr A. M. C. Dufus, of Roche Products Ltd, for the supply of indocyanine green dye. We also wish to thank Mr D. W. Blair, Mr N. A. Matheson, Mr G. E. Mavor and Mr W. Michie for permission to study patients under their care.

REFERENCES


Nous avons étudié les effets d'alcuronium (0,15 mg/kg de poids corporel) sur le rythme cardiaque, le volume pulso-taire, le débit du cœur, la pression artérielle moyenne et la résistance périphérique totale chez vingt-deux patients ventilés artificiellement, anesthésies avec 60 pourcent de protoxyde d‘azote dans de l‘oxygène, plus soit tubocurarine (25–35 mg suivant le poids corporel) et 0,2 pourcent de méthoxyflurane—série I, soit phénoperidine (1 mg/15 kg poids corporel)—série II. Le Pco₂ en fin de cycle était maintenu constant. L‘effet le plus remarqué fut une augmentation significative du rythme cardiaque chez les patients de la série II, accompagnée d‘une diminution significative du débit cardiaque et du volume pulsatoire. Il n‘y eut pas de modification significative de la pression artérielle moyenne, dans aucune des séries de patients; la réduction du débit cardiaque fut par conséquent accompagnée d‘une augmentation compensatoire de la résistance périphérique totale.