A CLINICAL COMPARISON OF AH8165 AND PANCURONIUM AS MUSCLE RELAXANTS IN PATIENTS UNDERGOING CARDIAC SURGERY

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SUMMARY

The non-depolarizing muscle relaxant AH8165 has been compared at two doses (0.5 and 1.0 mg/kg) with pancuronium (0.1 mg/kg) during induction of anaesthesia for patients having major cardiac surgery. After barbiturate-opiate premedication and thiopentone induction, administration of pancuronium was followed by no significant alteration in heart rate or arterial pressure. Both doses of AH8165 were followed by significant tachycardia, and the higher dose by arterial hypotension. The lower dose of AH8165 was unsatisfactory for tracheal intubation, but the AH8165 1 mg/kg gave intubating conditions similar to those with pancuronium 0.1 mg/kg.

The undesirable side effects of suxamethonium are largely related to its depolarizing action on the motor end-plate and its post-ganglionic parasympathomimetic actions. Research has therefore been directed to finding a drug of similar onset and duration to suxamethonium, but of a non-depolarizing type. At the same time, an effort has been made to replace tubocurarine with a drug which lacks its histamine-releasing and ganglion-blocking properties. Drugs of apparently shorter action than tubocurarine, such as gallamine (Riker and Wescoe, 1951; Walts and Prescott, 1965) and dacuronium (Feldman and Tyrrell, 1970), cause tachycardia, while dipyridamidium caused a variable duration of paralysis with no advantages over older drugs (Mushin and Mapleson, 1964).

AH8165 is a non-depolarizing muscle relaxant which has a rapid and brief action in animals (Baird and Reid, 1967). Unfortunately, clinical studies have shown that this drug is not as satisfactory as suxamethonium for rapid tracheal intubation (Arora et al., 1973; Young, Clarke and Dundee, 1975). Furthermore, its duration of action appears to be similar to the other non-depolarizing relaxants (Simpson et al., 1972; Arora et al., 1973).

A significant degree of arterial hypotension was observed by Arora and his colleagues (1973) following administration of AH8165 1 mg/kg body weight. This is not found when using pancuronium (Baird and Reid, 1967; McDowell and Clarke, 1969), and it was considered desirable to compare AH8165 with pancuronium under controlled conditions. Induction of anaesthesia in cardiac surgical patients provides these conditions (Lyons and Clarke, 1972) and such patients are a group in whom cardiovascular stability is essential. In the present study, AH8165 has been compared at two doses (0.5 and 1.0 mg/kg) with pancuronium bromide (0.1 mg/kg) and data relating to other relaxants given under similar conditions are available from the study by Lyons and Clarke (1972).

METHOD

Sixty patients scheduled for cardiac surgery were studied. They were divided into three groups of 20 according to the relaxant to be given. The management of such patients has been described in detail by Lyons and Clarke (1972). In those patients who were fully digitalized before operation, digoxin therapy was stopped before operation and, in general, those patients not previously digitalized were given digoxin for 24 hr before operation. The patients were premedicated with pentobarbitone 100 mg given orally 2 hr before operation, followed by morphine 0.14 mg/kg and hyoscine 0.2 mg i.m. 1 hr before operation. With this premedication, the patients arrived in theatre calm, sedated and sometimes asleep, but no evidence of significant cardiovascular or respiratory depression has been found with this regime (Lyons, Clarke and Vulgaraki, 1975). Under local anaesthesia, an intravenous infusion was set up and a cannula (No. 18 Medicut) was inserted into a radial artery. The e.c.g. and the arterial pressure waveform were displayed on an
oscilloscope (Cardiac Recorders) and a permanent record was obtained (Philips Cardiopan 3M).

Induction of anaesthesia was with thiopentone 4.5 mg/kg body weight followed by administration of oxygen 100% or air, for 3 min. At the end of 3 min, the muscle relaxant was given (table I) and assisted ventilation was started with 60% nitrous oxide in oxygen. Tracheal intubation was performed at 6 min. Arterial pressure and the e.c.g. were recorded continuously for 10 min after administration of thiopentone, and samples of arterial blood for gas analysis were taken at 1-min intervals for the first 6 min (until endotracheal intubation was performed).

Intubating conditions were noted and classified according to the scheme of Lund and Stovner (1962):

Excellent: Well separated cords, not moving, no bucking on the tube.

Satisfactory: Slight movement of the cords when touched, only slight bucking for a short period after intubation.

Fair: Conditions less favourable than in the previous categories, but still permitting intubation.

RESULTS

The three groups were comparable as regards age, weight and cardiac lesion (table I).

Arterial pressure.

The findings in table II and figure 1 show similar changes to those described by Lyons and Clarke (1972). There was a highly significant reduction in arterial pressure after the injection of thiopentone in all three groups, but little further decrease during the 3 min after administration of pancuronium 0.1 mg/kg body weight. Tracheal intubation in the pancuronium group was followed by an increase in mean arterial pressure to a value higher than the original pressure. AH8165 0.5 mg/kg body weight led to a significant decrease in arterial pressure (paired t test between 3rd and 6th min; t=3.40; P<0.005). The larger dose of AH8165 was followed by a highly significant decrease in pressure over the next 3 min (t=4.30; P<0.001). With both doses of AH8165, the mean arterial pressure increased following tracheal intubation, but 10 min after induction was still lower than the initial value.

Heart rate.

The heart rate in the group receiving pancuronium increased after thiopentone and there was a further significant increase after the muscle relaxant (t=3.29; P<0.005). There was a maximum increase after tracheal intubation. The group receiving AH8165 0.5 mg/kg had the highest initial heart rate, but there was a further significant increase between 3 and 6 min (t=6.07; P<0.001). The 1.0 mg/kg dose of AH8165 produced a marked tachycardia with a mean increase in rate of 26 beats/min between 3 and 6 min (t=6.52; P<0.001).

Arterial $P_{\text{aco}}$.

$P_{\text{aco}}$ was measured to assess whether the patients were being significantly hyper- or hypo-

<table>
<thead>
<tr>
<th>Muscle relaxant</th>
<th>Dose (mg/kg)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>1 valve</th>
<th>2 valves</th>
<th>Congenital</th>
<th>Mitral valvotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH8165</td>
<td>0.5</td>
<td>44</td>
<td>62</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>AH8165</td>
<td>1.0</td>
<td>37</td>
<td>59</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1</td>
<td>42</td>
<td>64</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table II. Mean (±SEM) of mean arterial pressure (mm Hg) and heart rate (beats/min) in patients receiving thiopentone 4.5 mg/kg at min 0, followed by AH8165 or pancuronium at 3 min and laryngoscopy and tracheal intubation at 6 min.
AH8165 AND PANCURONIUM IN CARDIAC SURGERY

Table IV. Intubating conditions following the two different doses of AH8165 and pancuronium classified according to the scheme of Lund and Stovner (1962). Number of patients in each category.

<table>
<thead>
<tr>
<th></th>
<th>AH8165 0.5 mg/kg</th>
<th>AH8165 1.0 mg/kg</th>
<th>Pancuronium 0.1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>2</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>9</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fair</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

between conditions after pancuronium and AH8165 1 mg/kg in this study.

Cardiac rhythm.

The presence of ventricular arrhythmias after administration of the muscle relaxant and endotracheal intubation was noted. In the three groups, between one and three patients had occasional ectopic beats, but in no group were these classified as “frequent”. Two patients receiving pancuronium developed transient bigeminal rhythm.

DISCUSSION

AH8165 in a dose of 1.0 mg/kg body weight, when given to patients with serious cardiac disability, produced marked cardiovascular changes. The degree of arterial hypotension was statistically significant and, while probably not clinically harmful, would seem to be undesirable when taken in conjunction with the marked tachycardia. The reduction in arterial pressure with this dose of AH8165 was less than with tubocurarine 0.5 mg/kg or alcuronium 0.25 mg/kg given under similar conditions (Lyons and Clarke, 1972), but the tachycardia both before and after tracheal intubation was greater. Studies by Loh (1970) and Kelman and Kennedy (1971) suggested that pancuronium had no effect on total peripheral resistance, but that a vagolytic action caused moderate tachycardia and hypertension. The patients in the present study, perhaps because they were partly digitalized, had only a small and not significant increase in heart rate. The two groups who received AH8165 had marked tachycardia in the presence of a decreasing arterial pressure which could be explained as a compensatory reaction to peripheral dilatation but, being more marked than the reaction with tubocurarine, may also involve inhibition at the vagal nerve endings in the heart. The findings of Bogg and his colleagues (1973), while difficult to interpret because of the preliminary administration of atropine, also showed a reduction in arterial pressure and sustained tachycardia with AH8165.
The cardiovascular changes following administration of muscle relaxants could be attributed to onset of IPPV rather than to the drug itself. This explanation cannot be excluded as a factor, but from the blood-gas measurements it is clear that significant alveolar hypo- or hyperventilation did not occur between 3 and 6 min. This study is a comparison of relaxants under clinical conditions; clearly, when pancuronium is given, any specific actions on the heart almost counterbalance possible effects of IPPV. This is not the case with AH8165 or with the muscle relaxants studied previously, tubocurarine and alcuronium (Lyons and Clarke, 1972).

The intubating conditions following the larger dose of AH8165 and pancuronium were not significantly different, but AH8165 0.5 mg/kg was unsatisfactory for this purpose. There was no indication of any advantage in rapidity of onset of action or completeness of muscle relaxation to offset the cardiovascular effects of the drug.

ACKNOWLEDGEMENTS
During this work Dr H. S. A. Young was supported by a grant from Allen and Hanbury Research Ltd. We are grateful to Dr K. Fidler of Glaxo Pharmaceutical Ltd for help and generous supplies of AH8165, also to Mr Alan Caulfield, A.S.C.T., for technical help during induction of anaesthesia.

REFERENCES
Ahí se comparó el relajante muscular no despolarizante AH 8165 en dos dosis (0,5 y 1,0 mg/kg) con pancuronium (0,1 mg/kg) durante inducción de anestesia para pacientes a los que se practicó cirugía cardiaca importante. En pacientes que sufrieron cirugía cardiaca, la administración de pancuronium fue seguida por una alteración insignificante en el ritmo cardiaco o presión arterial. Ambas dosis de AH 8165 fueron seguidas de taquicardia significativa, y la dosis más alta por hipotensión arterial. La dosis más baja de AH 8165 no dio buenos resultados para intubación traqueal, pero 1 mg/kg de AH 8165 dio condiciones de intubación semejantes a las de 0,1 mg/kg de pancuronium.

**ERRATA**

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Page 533, right-hand column, line 6: "(Galindo, 1969)" should read "(Galindo, 1971a)."

Page 535, left-hand column, line 27: "Liley, 1950" should read "Liley, 1956."