HAEMODYNAMIC EFFECTS OF VECURONIUM, PANCURONIUM AND ATRACURIUM IN PATIENTS WITH CORONARY ARTERY DISEASE

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Shortly after its introduction to anaesthetic practice, pancuronium was used to block neuromuscular transmission in poor risk patients, including those about to undergo cardiac surgery. Although not devoid of adverse haemodynamic effects (Kelman and Kennedy, 1971; Stoelting, 1972), pancuronium was advocated for patients undergoing coronary artery bypass grafting (Heinonen and Yvijarvi, 1980) and has been used widely during this operation (Stanley, Philbin and Coggins, 1979; Stanley et al., 1980; Quinton et al., 1981). The increase in heart rate produced by pancuronium has been considered acceptable in comparison with the histamine release (Comroe and Dripps, 1946; McIntosh and Paton, 1949), ganglion blockade and tachycardia (Smith and Whitcher, 1967; Kennedy and Kelman, 1970) produced by some of its competitors.

In equipotent doses vecuronium and atracurium have similar durations of action which are shorter than that of pancuronium (Agoston et al., 1980; Marshall, Agoston et al., 1980; Payne and Hughes, 1981). While vecuronium depends, like pancuronium, on renal and hepatic mechanisms to terminate its action, atracurium is broken down spontaneously in the plasma by Hofmann elimination and ester hydrolysis. Both agents have been shown to provide a high degree of cardiovascular stability when studied in animals and man (Marshall, McGrath et al., 1980; Payne and Hughes, 1981; Philbin et al., 1983).

Therefore, we decided to compare the haemodynamic effects of atracurium and vecuronium with those of pancuronium in patients about to undergo aorto-coronary bypass grafting. Evidence of histamine release was sought in relation to the use of atracurium.

PATIENTS AND METHODS

With the approval of the local Ethical Committee, 30 adult patients scheduled for coronary artery bypass surgery (CABG) were studied. Patients with a left ventricular ejection fraction of less than 0.50, or with any hepatic, renal or neuromuscular...
disorder were excluded. The majority of the patients were receiving nitrates, propranolol and nifedipine during the 3 days before surgery and all drugs were discontinued after the dose at 22.00 h on the evening before surgery. Premedication consisted of pentobarbitone 100 mg by mouth 2 h before anaesthesia, and morphine 10 mg and hyoscine 0.2 mg i.m. 1 h later. Peripheral, jugular venous and radial arterial cannulations were performed under local anaesthesia, and an ECG monitor (Hewlett-Packard 78205C) attached before the induction of anaesthesia.

A triple-lumen thermodilution flotation catheter was passed into the pulmonary artery for the measurement of central venous (CVP), pulmonary artery (PAP) and pulmonary capillary wedge (PCWP) pressures. Cardiac output (CO) was determined (thermodilution) using iced injectate. All measurements were obtained in triplicate with less than 10% variation using a cardiac output computer (Edwards Laboratories 9520A).

Following the attachment of the monitoring devices a 15-min period was allowed for stabilization of the cardiovascular system, after which baseline measurements were obtained. Anaesthesia was then induced by the injection (over 10 s) of diazepam 0.3 mg kg\(^{-1}\). (All drugs were injected to a freely-running infusion in the external jugular vein.) Patients received dextrose-saline solution 50–100 ml over the period of the study. Five minutes later, the eyelash reflex having been lost, neuromuscular blockade was produced by the i.v. injection over 5 s of approximately equipotent doses (Gramstad and Lilleaesen, 1982) of pancuronium (0.1 mg kg\(^{-1}\)), vecuronium (0.1 mg kg\(^{-1}\)) or atracurium (0.5 mg kg\(^{-1}\)), allocated to patients by use of a table of random numbers.

Eleven minutes after the induction of anaesthesia, fentanyl 25 \(\mu\)g kg\(^{-1}\) was given and tracheal intubation accomplished 1 min later. The degree of neuromuscular blockade was assessed with a train-of-four stimulus delivered to the ulnar nerve at the wrist, via surface electrodes, from a peripheral nerve stimulator (Myotest Biometer Limited). From the preanaesthetic period to the end of the study, the patients breathed oxygen via a non-rebreathing circuit, ventilation being assisted as required to maintain normocarbia. Surgery was not started before the end of the study period.

Cardiovascular measurements were recorded continuously (Hewlett-Packard Optical Recorder) for 25 min from time zero. Mean systemic, pulmonary and venous pressures were obtained by electronic integration of the haemodynamic wave forms. Cardiac output and arterial blood-gas tensions were measured at 0, 3, 6, 9, 15 and 20 min. The measurements were used to calculate cardiac index (CI), and systemic and pulmonary vascular resistances (SVR, PVR).

In assessing the effects of the individual neuromuscular blockers on cardiovascular variables in the time period after their administration, the results have been subjected to repeated measures analysis of variance. When drugs were compared, account was taken of differences in the variables at baselines by using the 3-min results as covariates in the analyses of variance.

In order not to obscure the small cardiovascular changes which might occur after the administration of the neuromuscular blockers by the much larger, and possibly more variable, changes resulting from the administration of fentanyl, two analyses were performed for each variable. The first included results in the 6–11 min period only, while the second included additionally the results obtained at 15 and 20 min.

Where statistically significant effects were observed in the analysis of variance, means were compared using the appropriate standard errors derived from the analysis of variance.

**RESULTS**

Details of the three groups of patients are summarized in tables I and II; these are broadly comparable with regard to weight, body surface area, age, sex and previous drug therapy.

All patients received diazepam 0.3 mg kg\(^{-1}\) for induction of anaesthesia at time 0, and in comparing the haemodynamic effects of the neuromuscular blocking drugs, values 3 min after induction have been regarded as the baseline. At this time one-way analysis of variance showed that there were no significant differences between the groups for any of the variables except PCWP (\(P < 0.05\)), which was greater in the atracurium group than in the other two groups.

The analyses of heart rates (HR) between 6 and 11 min showed evidence (\(P < 0.025\)) of a different effect between the drugs, but the heart rate (fig. 1) which behaved in a similar manner with time (fig. 1). This suggests that there were differences in heart rate during this period between the three drugs after adjustment for baseline readings, and
HAEMODYNAMIC EFFECTS OF NEUROMUSCULAR BLOCKERS

TABLE I. Physical characteristics of patients (mean ± SEM)

<table>
<thead>
<tr>
<th>Neuromuscular blocker</th>
<th>Body weight (kg)</th>
<th>Age (yr)</th>
<th>Body surface area (m²)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>66.8 ± 5.82</td>
<td>61.0 ± 5.05</td>
<td>1.72 ± 0.11</td>
<td>7</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>73.5 ± 6.39</td>
<td>53.6 ± 6.37</td>
<td>1.85 ± 0.10</td>
<td>8</td>
</tr>
<tr>
<td>Atracurium</td>
<td>70.0 ± 4.26</td>
<td>51.6 ± 5.79</td>
<td>1.77 ± 0.08</td>
<td>8</td>
</tr>
</tbody>
</table>

TABLE II. Previous drug treatment of patients (10 in each group)

<table>
<thead>
<tr>
<th>Relaxant group</th>
<th>Number of patients receiving</th>
<th>Nitrates</th>
<th>Propranolol</th>
<th>Nifedipine</th>
<th>Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Atracurium</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

the differences were maintained throughout the period. Pancuronium and atracurium produced significant increases in the HR during this period compared with the 3-min baseline. Following the administration of fentanyl the decrease in HR at 15 and 20 min was significant compared with baseline in the patients receiving vecuronium (P < 0.05). Two patients in this group had heart rates less than 40 beat min⁻¹.

There were no significant differences at 6 and 9 min in intravascular pressures (table III) between the three groups after adjusting for differences at baseline. Following the administration of fentanyl there were marked decreases in MAP and PAP in all groups.

There was a significant interaction between the myoneural blockers and time for cardiac index (P < 0.025). This indicates a difference in the pattern of the changes in cardiac index over the 6-min period in the three groups. An increase in CI in the atracurium group at 6 min had returned to near baseline values by 9 min. In contrast, the increase in CI in the pancuronium group did not occur until 9 min. At both 6 and 9 min the CI following vecuronium had decreased slightly (ns) from the baseline readings.

Although the interaction between the neuromuscular blockers and time in the analysis of variance of SVR was not significant

![Fig. 1. Heart rates in the three groups of patients after induction of anaesthesia.](image)

- - - - - = Pancuronium; ▲-▲-▲ = vecuronium; ○-○-○ = atracurium.
(0.05 < \( P < 0.1 \)), examination of the mean at 6 min showed a highly significant decrease in the atracurium group (\( P < 0.001 \)). Other derived variables showed no significant changes between the groups or within each group until after the administration of fentanyl.

Nine out of 10 patients in the atracurium group developed skin flushes of varying degrees of severity immediately after receiving the drug, with one patient also developing large skin weals (0.5—1.0 cm diameter) widely distributed over his body. No patients showed any signs of bronchospasm and the skin changes faded spontaneously within 20 min of their appearance. No evidence of any skin or systemic changes suggestive of histamine release was seen in either the vecuronium or pancuronium groups.

**DISCUSSION**

The cardiovascular effects of pancuronium are well recognized: it has been shown to induce small increases in HR, CO and MAP (Kelman and Kennedy, 1971; Lyons and Clarke, 1972), but these have been regarded as at worst acceptable or at best a positive advantage, countering any tendency for these variables to decrease as anaesthesia is induced. The causes of these effects are thought to be a combination of post-ganglionic vagal blockade (Saxena and Bonta, 1970) and the blocking of noradrenaline re-uptake (Domenech et al., 1976). Although the changes in HR seen with pancuronium may be marked in certain patients, the lack of histamine release and of ganglionic blockade have ensured its popularity in cardiovascular anaesthesia. Despite this, the combination of pancuronium and metocurine has been advocated to minimize the changes in HR (McDonald and Zaidan, 1984). Fentanyl—pancuronium anaesthesia has also been advocated for patients undergoing CABG because of the lack of neuroendocrine stress response and subsequent haemodynamic stability (Stanley, Philbin and Coggins, 1979; Stanley et al., 1980; Quinton et
The present findings confirm that pancuronium tends to cause a moderate increase in HR with a small increase in CI which returns to pre-relaxant values upon the administration of fentanyl. By not inducing such an increase in HR, vecuronium, as anaesthesia deepens, allows the CI to decrease, although this did not attain statistical significance.

In a comparison of a variety of non-depolarizing neuromuscular blockers, Marshall, McGrath and colleagues (1980) and Booij and colleagues (1980) reported no significant cardiovascular changes with vecuronium, in contrast to the significant increases in HR, MAP, PCWP and CI found with pancuronium. Using vecuronium in a patient group similar to those in the present study, Morris and colleagues (1983) showed no significant changes in HR, MAP and PCWP, but a small though significant increase in CO, and decrease in SVR. However, they used a larger dose of the drug (0.28 mg kg\(^{-1}\)) and this may explain the differences between their results and those reported here. Allowing for the differences in dose and the fact that only five of seven patients were receiving beta-blocking drugs, the results of both studies are in broad agreement and support the conclusion that vecuronium has little effect on the cardiovascular system and is better than pancuronium at maintaining cardiovascular stability.

The lack of any chronotropic effect with vecuronium may allow the HR to decrease to unacceptably low values. This situation is more likely to be encountered in patients who are clinically adequately controlled on beta-blocking drugs such as is commonly the case in coronary artery surgery (Sill et al., 1984). The deep levels of anaesthesia produced by the high-dose fentanyl technique have been shown to block the stimulating effects of tracheal intubation (Bennett and Stanley, 1980). Such profound anaesthesia in beta-blocked patients coupled with the use of vecuronium probably requires a higher level of vigilance by the anaesthetist than when the heart rate is supported by the administration of pancuronium. This difficulty was foreseen by Savarese and Kitz (1973), who suggested that the relative bradycardia and hypotension caused by most modern anaesthetic techniques may make drugs with a mild vagal blocking effect more acceptable than a drug with a complete lack of cardiovascular effects. It remains to be seen whether the advantages shown by vecuronium plus any decrease in myocardial oxygen consumption which the drug may offer, will be sufficient to overcome the problems of marked bradycardia in certain patients in clinical practice. These findings are supported by the study of Salmenperä and colleagues (1983) who observed a significant decrease in HR and CO following vecuronium administered to patients anaesthetized with high-dose fentanyl. Despite the risk of atrioventricular dissociation or slow heart rate, they suggested that patients with limited coronary vascular reserve may benefit from the negative chronotropic effect of vecuronium.

Vecuronium bromide is supplied as a freeze-dried powder to be freshly dissolved before use. Atracurium besylate must be stored at between 2 and 5 °C to avoid spontaneous decomposition by Hofmann elimination. These requirements were adhered to during this study, atracurium besylate being injected to a continuously running infusion to an external jugular vein within 15 min of its removal from the refrigerator. The changes seen in the atracurium group suggest histamine release to a greater degree than has been seen in previous clinical studies with the drug (Hilgenberg, Stoelting and Harris, 1983). Basta and co-workers (1983) have shown that atracurium produces a two-fold increase in serum histamine concentration when given in a dose of 0.6 mg kg\(^{-1}\), while vecuronium, in a dose of 0.2 mg kg\(^{-1}\), induces no increase in histamine concentration. The decreases in MAP and SVR with the accompanying transient increases in HR and CI are suggestive of the release of histamine or other vasoactive substance. Sokoll and co-workers (1983) studying the haemodynamic effects of atracurium in patients undergoing nitrous oxide—enflurane anaesthesia, found no indication of histamine release and no untoward side effects on cardiovascular performance. Philbin and co-workers (1983), studied the effects of atracurium in patients undergoing coronary artery surgery and found significant decreases in MAP, but no change in CO or SVR. However, these results excluded one patient who, having received 0.3 mg kg\(^{-1}\) of the drug exhibited a "typical histamine response" with large increases in CO and a decrease in MAP.

The questions raised by the reported effects of atracurium in this and previous studies may decrease the use of the drug in patients in whom...
a high degree of haemodynamic stability is essential. However, tubocurarine is well known to produce more marked histamine release and, despite this, has remained popular in clinical practice for 40 years while not offering any of the advantages of lack of ganglionic blockade or short duration of action seen with atracurium.

Vecuronium, with its shorter duration of action and lack of cardiovascular stimulation, offers significant advantages over pancuronium. The wide margin of safety between the clinical dose and that producing significant cardiovascular side effects, allows the initial dose of the drug to be increased to give a duration of action comparable to that of pancuronium, should this be desired, without any tendency to develop side effects. Although the idea of a neuromuscular blocking drug without cardiovascular side effects is attractive, its use may result in heart rates that are slower than many anaesthetists consider acceptable.

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