CARDIOVASCULAR EFFECTS OF DOXACURIUM, PANCURONIUM AND VECURONIUM IN ANAESTHETIZED PATIENTS PRESENTING FOR CORONARY ARTERY BYPASS SURGERY†

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SUMMARY

The cardiovascular effects of bolus doses of doxacurium 0.037 mg kg⁻¹ were compared with those following equipotent doses of pancuronium (0.09 mg kg⁻¹) and vecuronium (0.075 mg kg⁻¹) and with those following high-dose doxacurium (0.075 mg kg⁻¹), in patients with coronary artery disease. Anaesthetic technique comprised premedication with lorazepam, papaveretum and hyoscine, induction with diazepam, fentanyl, thiopentone, atropine and suxamethonium, and the trachea was intubated. At least 20 min later, during stable nitrous oxide in oxygen anaesthesia, a single bolus of neuromuscular blocking drug was administered and the effects measured at 1, 5 and 10 min. There was a small decrease in heart rate following doxacurium 0.075 mg kg⁻¹, but no other significant or dose-related changes in mean heart rate, arterial pressure or cardiac index with doxacurium. Similar results were found following vecuronium, but the reduction in heart rate was more pronounced. In contrast, significant increases in mean arterial pressure, heart rate and cardiac index occurred after pancuronium.

KEY WORDS

Pancuronium has been advocated as the skeletal muscle relaxant of choice during anaesthesia for coronary artery bypass graft (CABG) surgery [1]. However, in some patients its vagolytic and sympathomimetic effects may cause myocardial ischaemia [2, 3]. Vecuronium, a pancuronium analogue, produces little haemodynamic change in patients undergoing CABG surgery and this drug may be preferable in patients with limited cardiac reserve [4]. However, the use of vecuronium in these circumstances may be associated, in some patients, with marked bradycardia [5].

Doxacurium chloride (BW A938U) is a new non-depolarizing neuromuscular blocking agent. It has a long duration of action, comparable to that of pancuronium [6]. The administration of doxacurium appears to cause minimal changes in heart rate or arterial pressure [6, 7]. The present study was designed to compare the haemodynamic effects of single bolus doses of doxacurium, pancuronium and vecuronium in anaesthetized patients undergoing CABG surgery.

PATIENTS AND METHODS

After approval from the Committee on Safety of Medicines and the local Ethics Committee, we studied 36 ASA Class III or IV adult patients undergoing elective CABG surgery. Each patient gave signed informed consent. Angiograms of the patients were viewed before operation and left ventricular function was assessed as good, moderate or poor. Patients with valvular disease requiring surgery, with poor left ventricular function or critical narrowing of the left main artery were excluded.


†Presented in part at The Anaesthetic Research Society, Warwick Meeting, April 7–8, 1989.
Coronary artery disease was excluded; other exclusions included a history of alcohol or drug abuse, clinically significant neuromuscular, hepatic, renal or psychiatric disease, exposure to histamine receptor (H1/H2) antagonists within 24 h before surgery, and a history of asthma. All routine cardiovascular and vasoactive medications were continued up to the morning of surgery. The first 27 patients studied were allocated randomly to receive an estimated 1.5 \times ED_{95} dose of doxacurium (0.037 mg kg\(^{-1}\); group 1), pancuronium (0.09 mg kg\(^{-1}\); group 2) or vecuronium (0.075 mg kg\(^{-1}\); group 3); the final nine patients studied received an estimated 3 \times ED_{95} dose of doxacurium (0.075 mg kg\(^{-1}\); group 4). Entry of patients into group 4 was deferred until the safety of doxacurium had been confirmed in the lower dose doxacurium group of patients (group 1).

Premedication consisted of oral lorazepam 2–4 mg, 90–120 min before and i.m. papaveretum 15–20 mg with hyoscine 0.3–0.4 mg 1 h before the patient arrived in the operating theatre, where they were monitored by ECG monitor (Kontron 304), and peripheral venous and radial artery cannulations were performed under local anaesthesia. Patients received i.v. diazepam 0.05–0.2 mg kg\(^{-1}\). A triple-lumen thermodilution pulmonary artery flotation catheter (Spectramed 9002) and two central venous catheters were inserted under local anaesthesia. Measurements of arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressures were made using Gould Statham P23 pressure transducers recalibrated against a mercury column; these were recorded on a Kontron 304 chart recorder, with lead II of the ECG. Cardiac output measurements were made in triplicate using iced injectate and a Gould SP 1432 cardiac output computer. The evoked gated integrated compound electromyogram (EMG) of the adductor pollicis muscle in response to supramaximal train-of-four (2 Hz for 2 s) stimulation of the ulnar nerve (train frequency 0.05 Hz; stimulus duration 0.1 ms) was recorded using surface electrodes and a Datex Relaxograph. Following preoxygenation, anaesthesia was induced with additional i.v. diazepam 5–10 mg, fentanyl 500 \mu g and thiopentone 50–500 mg titrated to the individual response of each patient. Anaesthesia was maintained with 50% nitrous oxide in oxygen. Neuromuscular monitoring was calibrated and stabilized before administration of suxamethonium 1 mg kg\(^{-1}\). Intubation was facilitated by spraying the larynx with 4% lignocaine. Administration of suxamethonium did not lead immediately to haemodynamic changes. However, at or shortly after laryngoscopy, seven of the first 10 patients developed profound bradycardia, requiring atropine. Subsequently, it was decided to administer atropine routinely at induction to all subjects. Following tracheal intubation, end-tidal carbon dioxide (Datex Normocap) was monitored, arterial blood-gas sampling was performed at regular intervals, and ventilation was adjusted to maintain normocapnia.

During stable anaesthesia, at least 15 min after intubation and following EMG confirmation of full recovery from suxamethonium-induced neuromuscular block, a single undiluted dose of doxacurium, pancuronium or vecuronium was injected as a rapid (5-s) bolus into a central vein. With the exception of cardiac output measurements, patients remained unstimulated from the time of intubation until at least 10 min following injection of the non-depolarizing neuromuscular blocking drug. After arrival of the patient in the operating theatre up to the end of the period of study, all patients received an i.v. infusion of compound sodium lactate solution 500 ml and up to 500 ml of Haemaccel.

Haemodynamic measurements were made immediately before induction of anaesthesia and at 5-min intervals after intubation of the trachea until vital signs were stable. The final recording in this sequence was defined as the baseline (pre-relaxant) recording, and immediately preceded administration of the non-depolarizing neuromuscular blocking agent. Further haemodynamic measurements were performed at 1, 5 and 10 min after administration of the non-depolarizing blocker. Variables recorded by later inspection of paper trace recordings included systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR; average of five R–R intervals), mean central venous pressure (CVP), mean pulmonary artery pressure (PAP) and mean pulmonary capillary wedge pressure (PCWP).

All intravascular pressure measurements were made at end-expiration. Cardiac output measurements represent the mean of three readings. Estimates of mean arterial pressure (MAP) and cardiac index (CI) were calculated from the measured haemodynamic variables using standard formulae.

Repeated measures analysis of variance on log-transformed data was used to assess the signifi-
cance of changes in haemodynamic variables over time. Haemodynamic data obtained before induction of anaesthesia were analysed independently using one-way analysis of variance and were not included in repeated measures analyses. Patient data were analysed using one-way analysis of variance or Fisher's exact test where appropriate. Comparisons were made between groups receiving equipotent doses of doxacurium, pancuronium or vecuronium (groups 1–3) and also between groups receiving doxacurium alone (groups 1 and 4). Statistical significance was taken at $P < 0.05$ (Huynh and Feldt correction [8] for data analysed by repeated measures analysis of variance).

RESULTS

The four patient groups were comparable in age, weight, height, body surface area (BSA) (table I) and preoperative exposure to routine cardioactive medications (table II). There were no significant differences between groups in induction doses of fentanyl, thiopentone or diazepam, or in mean doses of atropine received after induction. The average times between anaesthetic induction or administration of atropine and administration of the non-depolarizing neuromuscular blocker were similar for all groups (table III).

There were no significant differences between groups 1, 2 and 3 or between groups 1 and 4 in haemodynamic variables before administration of the myoneural blocker (table IV). In analysing groups 1, 2 and 3, significant increases over time were observed in MAP, HR and CI after pancuronium, and a decrease in HR after vecuronium. After doxacurium 0.037 mg kg$^{-1}$ (group 1) there were no significant changes with time in MAP, HR or CI. Significant decreases in CVP, PAP and PCWP were observed over time after equipotent doses of doxacurium, pancuronium and vecuronium, with no differences between groups. High dose doxacurium (0.075 mg kg$^{-1}$;
Table IV. Mean systemic arterial pressure (MAP), heart rate (HR), cardiac index (CI), central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP), before (baseline) and at 1, 5 and 10 min after administration of the myoneural blocker (mean (SEM)).

Group 1 = doxacurium 0.037 mg kg\(^{-1}\); group 2 = pancuronium 0.09 mg kg\(^{-1}\); group 3 = vecuronium 0.075 mg kg\(^{-1}\); group 4 = doxacurium 0.075 mg kg\(^{-1}\).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Baseline</th>
<th>1 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>73.9 (2.5)</td>
<td>72.8 (1.9)</td>
<td>75.4 (2.1)</td>
<td>74.6 (2.2)</td>
</tr>
<tr>
<td>HR (beat min(^{-1}))</td>
<td>59.4 (3.0)</td>
<td>58.7 (3.0)</td>
<td>58.3 (3.1)</td>
<td>57.9 (3.3)</td>
</tr>
<tr>
<td>CI (litre min(^{-1}) m(^{-1}))</td>
<td>2.26 (0.13)</td>
<td>2.34 (0.15)</td>
<td>2.50 (0.15)</td>
<td>2.29 (0.12)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>9.3 (1.9)</td>
<td>7.4 (1.1)</td>
<td>6.5 (0.8)</td>
<td>6.5 (0.8)</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>19.9 (2.1)</td>
<td>19.1 (1.7)</td>
<td>18.2 (1.7)</td>
<td>17.9 (1.7)</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>11.8 (1.7)</td>
<td>10.9 (1.6)</td>
<td>9.7 (0.7)</td>
<td>9.7 (0.8)</td>
</tr>
</tbody>
</table>

In order to illustrate further the changes in MAP and HR after doxacurium, pancuronium or vecuronium, the maximum changes in MAP and HR observed in each individual patient in the 10-min period after administration of the blocking drug, expressed as a percentage of the baseline value, were plotted graphically (fig. 2). Maximum changes in MAP and in HR did not necessarily occur at the same time. After doxacurium, although there is some degree of inter-patient variation, data points are generally clustered symmetrically around the origin, although a majority of patients in the high dose group demonstrated a reduction in HR. However, no
patient receiving doxacurium experienced a >20% increase or decrease in MAP or HR. In contrast, data points for pancuronium are distributed generally in the upper right quadrant, indicating increases in both HR and MAP. Two patients receiving pancuronium had >20% increases in both MAP and HR, and in two others, HR alone increased by >20%. Inter-patient variation was also more pronounced in patients who received vecuronium; most had a reduction in HR, and one patient a >20% decrease in both HR and MAP (fig. 2).

DISCUSSION

The study was designed to minimize interacting influences such as medical status, medication, anaesthetic drugs and surgical manipulation. Dose of induction agent was titrated to the individual response of each patient and suxamethonium was used to facilitate rapid tracheal intubation. This technique has been used in previous studies investigating the haemodynamic effects of neuromuscular blocking drugs [5, 9]. We have not found any report of bradycardia at laryngoscopy in other similar studies, although of the first 10 patients investigated, seven developed clinically significant bradycardia requiring administration of atropine at laryngoscopy or intubation. This included two patients with sinus node arrest at laryngoscopy. We cannot explain why our patients behaved differently from those in other studies, but on reviewing our initial experience we decided to administer atropine at induction to the remaining 26 patients in the study. As the effect of

![Graph showing changes in MAP and HR over time after injection of doxacurium and pancuronium](image-url)

**FIG. 1.** Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration of doxacurium 0.037 mg kg\(^{-1}\) (○), doxacurium 0.075 mg kg\(^{-1}\) (●), pancuronium 0.09 mg kg\(^{-1}\) (□) or vecuronium 0.075 mg kg\(^{-1}\) (△).

![Graph showing maximum changes in MAP and HR after administration of doxacurium and pancuronium](image-url)

**FIG. 2.** Maximum % changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) observed at 1, 5 and 10 min after administration of doxacurium 0.037 mg kg\(^{-1}\) (○), doxacurium 0.075 mg kg\(^{-1}\) (●) (1.5 and 3.0 × ED\(_{95}\) values, respectively), pancuronium 0.09 mg kg\(^{-1}\) (□) or vecuronium 0.075 mg kg\(^{-1}\) (△). Each point represents data from a single patient.
i.v. atropine on HR persists for 6 h or longer in unpremedicated awake healthy individuals [10], it seems likely that its administration may have influenced the haemodynamic changes observed after administration of neuromuscular blocking drug in this study. However, as the mean dose of atropine and the mean time interval between administration of atropine and non-depolarizing blocker were similar in all groups, the influence of atropine was probably also similar in all groups.

Doxacurium in doses of 0.037 mg kg$^{-1}$ and 0.075 mg kg$^{-1}$ was thought to represent approximate 1.5 and 3.0 $\times$ ED$_{95}$ multiples, based upon an ED$_{95}$ estimate for doxacurium of 0.025 mg kg$^{-1}$ [11]. The doses of pancuronium and vecuronium selected for use were approximately equipotent to doxacurium 1.5 $\times$ ED$_{95}$, based on ED$_{95}$ values estimated by single-dose methodology during opioid anaesthesia [12-14].

Our study has demonstrated that doxacurium was a cardio-stable neuromuscular blocking agent in patients with significant coronary artery disease when administered under the conditions described. This stability has been described by other workers both in healthy patients [6, 7] and in those with significant coronary arterial or valvular heart disease [9].

Several workers have reported increases in HR, MAP and CO after administration of pancuronium [4, 5, 15, 16] and our results are in general agreement. It is worth noting that the prior administration of atropine in the present study did not prevent an increase in HR after pancuronium, contrary to the suggestion of Kelman and Kennedy [15]. However, two of the nine patients in the pancuronium group did not receive atropine and in both patients a >20% increase in HR was observed. Atropine may, therefore, attenuate pancuronium-induced increases in HR, presumably by modification of the inhibition by pancuronium of vagal muscarinic receptors, but was unable to prevent these increases under the conditions of the present study.

Vecuronium has been found to be relatively free from direct haemodynamic side effects [4, 16]. However, intraoperative bradycardia after vecuronium has been described [17], and it is thought to result from lack of antagonism of vagotonic influences such as anaesthetic drugs and surgical manoeuvres. With the exception of fentanyl, administered at least 20 min before the study drug, these influences were absent during the period of study, yet a decrease in HR was observed after vecuronium and high-dose doxacurium. A significant reduction in HR (9.1%) following vecuronium during fentanyl anaesthesia in patients presenting for CABG surgery compared with a smaller reduction (3.8%) in control patients who did not receive a neuromuscular blocking agent led Salmenpera and colleagues [5] to suggest that other factors, such as onset of neuromuscular block per se, may have been responsible for the reduction in HR after vecuronium. This mechanism may account for the differences in HR changes observed in patients receiving vecuronium and doxacurium in the present study, as the onset time of a 1.5 $\times$ ED$_{95}$ dose of doxacurium is longer than that of vecuronium 0.075 mg kg$^{-1}$ and doxacurium 0.075 mg kg$^{-1}$ [6, 18].

ACKNOWLEDGEMENTS

The authors thank Mr S. Evans for assistance with statistical analyses, and also the Department of Clinical Therapeutics, The Wellcome Research Laboratories, Beckenham, Kent, for continued support. Doxacurium chloride was supplied by The Welcome Research Laboratories.

REFERENCES


Hemodynamic effects of doxacurium chloride in patients re...


