Cardiovascular effects of non-depolarizing neuromuscular blockers in patients with coronary artery disease

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To compare haemodynamic responses associated with equipotent doses of muscle relaxants and high dose fentanyl (50 $\mu g \cdot kg^{-1}$), 40 non-hypertensive patients who were receiving beta adrenergic and calcium channel blocker therapy and undergoing coronary bypass surgery were randomized to four study groups receiving the following: (1) atracurium: 0.4 $mg \cdot kg^{-1}$, (2) pancuronium: 0.12 $mg \cdot kg^{-1}$, (3) vecuronium: 0.12 $mg \cdot kg^{-1}$, or (4) pancuronium–metocurine mixture: (0.4 mg + 1.6 $mg \cdot ml^{-1}$):1 ml/10 kg. Neuromuscular blockers were injected with fentanyl at induction. Haemodynamics were recorded with the patients awake (baseline), at two minutes post-induction, and at two and five minutes after intubation.

Pancuronium was the only drug associated with significant increases in HR; no other significant changes occurred within each group when compared to their respective baseline haemodynamics. HR increased more after induction with pancuronium when compared to atracurium (23 vs. 4 per cent, $p < 0.05$) and to vecuronium (23 vs. 2 per cent, $p < 0.05$), and when compared to vecuronium after intubation (29 vs. 7 per cent, $p < 0.05$). The pancuronium–metocurine mixture caused tachycardia which was less than, though not significantly different than with pancuronium; however, HR returned to baseline by five minutes with the mixture, but remained elevated with pancuronium (3 vs. 18 per cent, $p < 0.05$). SVR fell more on induction with atracurium when compared to vecuronium (−18 vs. 1 per cent, $p < 0.05$). These changes in HR or SVR were not accompanied by ECG signs of ischaemia. Vecuronium was associated with the most stable overall haemodynamic course at all measurement times. In general, intubating doses of the neuromuscular blockers studied appeared safe for use in patients with coronary artery disease.

Key words

NEUROMUSCULAR RELAXANTS: pancuronium, vecuronium, atracurium, metocurine; ANAESTHETICS INTRAVENOUS: fentanyl; ANAESTHESIA: cardiovascular.

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Cardiovascular effects of non-depolarizing neuromuscular blockers are important in the anaesthetic management of patients, particularly those undergoing cardiac surgery.[1] Their administration may be associated with haemodynamic changes, related to histamine release or effects on the autonomic nervous system.[2] To avoid undesirable haemodynamic effects, combinations of muscle relaxants have been examined which permit lower doses, with a reduction of dose-dependent cardiovascular effects.[3] Recently, the new competitive neuromuscular blocking agents, atracurium and vecuronium, have been shown to provide adequate muscle relaxation without significant haemodynamic effects in healthy subjects and patients with coronary artery disease.[4] The present investigation was undertaken to compare the cardiovascular effects of vecuronium, atracurium and a pancuronium–metocurine mixture to those of pancuronium, when used with high dose fentanyl anaesthesia in non-hyper-

tensive patients with coronary artery disease, who were receiving chronic beta adrenergic and calcium channel blocker therapy.

Methods

After informed consent, 40 patients (mean age: 55 years; 35 male) were studied according to a protocol approved by the Human Subjects Committee. All patients had coronary artery disease (greater than 50 per cent diameter narrowing in each of one to three vessels), and were scheduled for elective coronary artery bypass surgery. All patients were in sinus rhythm. Twenty-three subjects showed ECG signs of remote myocardial infarction. Excluded from the study were patients with known arterial hypertension, valvular heart disease, significant liver and kidney disease (defined as serum bilirubin and creatinine levels greater than twice normal, respectively) and those who were clinically unstable (NYHA Class IV). Beta adrenergic and calcium channel blocker therapy were continued up to the morning of surgery.

Patients were premedicated with morphine 0.1 $mg \cdot kg^{-1}$ IM, scopolamine 0.4 mg IM and topical nitroglycerin 5 or 10 mg. In each patient, a 20-gauge cannula was inserted in a radial artery, and a triple lumen flow directed pulmonary artery catheter was introduced into the pulmonary artery.

The 40 patients were allocated randomly to four study groups and each group received one of the following: (1) pancuronium 0.12 $mg \cdot kg^{-1}$ IV; (2) vecuronium 0.12 $mg \cdot kg^{-1}$ IV; (3) atracurium 0.4 $mg \cdot kg^{-1}$ IV; or (4) pancuronium–metocurine mixture (0.4 mg + 1.6 $mg \cdot ml^{-1}$):1 ml/10 kg IV. Anaesthesia was induced with fentanyl 50 $\mu g \cdot kg^{-1}$ and 100 per cent O_2. Twenty per cent of the calculated neuromuscular blocker dose was given initially to avoid fentanyl-induced rigidity; thereafter, the remaining drug and fentanyl were given together. The mean duration of fentanyl injection was three minutes. Patients were intubated after the post-induction measurements were completed. No other drugs were given during the study period.

Baseline (awake) haemodynamic measurements were made five minutes after insertion of intravascular catheters. Measurements at end expiration were repeated 2 minutes after induction, and at two and five minutes following intubation. Pressures were measured with transducers zeroed at the mid-axillary line. Systemic, pulmonary arterial and central venous pressures, electrocardiogram lead V5 and the patient's clinical condition were monitored continuously, and electrocardiogram limb leads intermittently.

Haemodynamic measurements were recorded using a computer which was programmed to record pressures and heart rate at specific points of measurement. Cardiac outputs were measured by thermodilution and expressed as the mean from two well-formed curves agreeing within ten per cent. Haemodynamic indices were calculated by computer from pressure and cardiac output measurements, according to standard formulae.

Ventilation was assisted manually using 100 per cent oxygen and a mask and, following intubation, controlled with 100 per cent oxygen using the non-rebreathing circuit of an Engstrom ventilator. Respiratory rate and tidal volume were adjusted to maintain $PaCO_2$ at about 40 mmHg.

Statistical evaluation was by analysis of variance, with $p < 0.05$ considered to be significant. For differences between the four drug groups at the same measurement time, a one-way ANOVA was performed, followed by t-tests when F was significant. For differences between various measurement times and baseline within the same drug group, a one-way repeated measures ANOVA was performed, followed by paired t-tests when F was significant.

Results

The patients in the four study groups were comparable for age, sex, body weight, history of preoperative myocardial infarction, degree of coronary artery disease, and preoperative beta blocker and calcium channel blocker therapy (Table I). Similarly, there were no significant differences in baseline haemodynamics between groups (Table II). Cardiovascular responses to induction and intubation are summarized in Table II.

On induction, no significant haemodynamic changes occurred in any group when compared to that group's baseline values. Comparison between groups showed that the per cent increase in HR in patients who had received fentanyl–pancuronium was significantly greater than that observed in patients who had received fentanyl–vecuronium (23 vs 2 per cent, $p < 0.05$) and in those who had received fentanyl–atracurium (23 vs. 4 per cent, $p < 0.05$) (Figure 1). Patients receiving fentanyl–

TABLE I Preoperative data*

	Atracurium	*Vecuronium*	*Pancuronium*	*Pancuronium–metocurine mixture*
Age (yr)	55 ± 6	55 ± 7	56 ± 7	56 ± 5
Male	9	10	8	8
Weight (kg)	78 ± 5	78 ± 8	82 ± 9	80 ± 25
β-blocker	5	6	6	3
Ca-antagonist	2	5	2	3
Remote MI	6	7	5	5

*Number of patients or mean values ± SD.
n = 10 in each group.

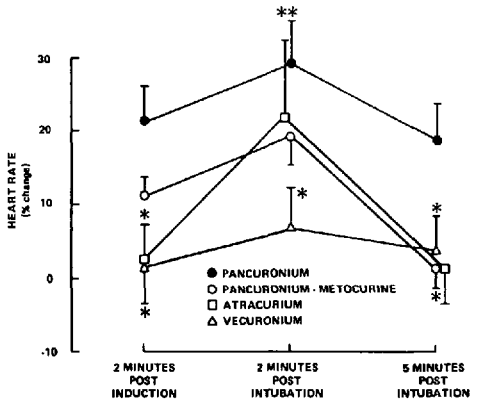

FIGURE 1 Effects of vecuronium (0.12 mg·kg^{-1}), pancuronium (0.12 mg·kg^{-1}), atracurium (0.4 mg·kg^{-1}) and pancuronium–metocurine mixture (0.4 mg + 1.6 mg·ml^{-1}:1 ml/10 kg) on per cent change in heart rate in patients with coronary artery disease. All patients received concomitant fentanyl (50 μg·kg^{-1}). Each symbol and bracket represents the mean ± SE in ten patients. Asterisk (*) indicates a significant difference when compared to pancuronium at the measurement time indicated. Asterisks (**) indicate a significant difference from baseline heart rate.

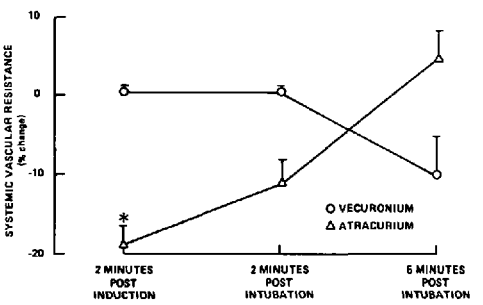

FIGURE 2 Effects of vecuronium (0.12 mg·kg^{-1}) and atracurium (0.4 mg·kg^{-1}) on per cent change in SVR in patients with coronary artery disese. Fentanyl (50 μg·kg^{-1}) was given with the relaxant. Each symbol and bracket represents the mean ± SE in ten patients. Asterisk (*) indicates a significant difference between the two groups at the time indicated.

atracurium, as a group showed a significantly greater fall in SVR after induction, when compared to those receiving fentanyl–vecuronium (−18 vs. 1 per cent, $p < 0.05$) (Figure 2). Changes in other haemodynamic measurements were not significantly different between the study groups.

Intubation in the fentanyl–pancuronium group caused a further increase in mean HR which was now significantly higher (29 per cent, $p < 0.05$) than baseline values (Figure 1). Increases in HR over basal values were also seen after intubation in patients who had received fentanyl with atracurium or the pancuronium–metocurine mixture (24 and 19 per cent respectively, $p > 0.05$). This tachycardia returned close to baseline values by five minutes. The most stable haemodynamic response to intubation occurred with vecuronium.

Comparison between groups showed that the per cent increase in HR was significantly larger in patients receiving fentanyl–pancuronium than in those who had received fentanyl–vecuronium; this was so two minutes after intubation (29 vs. 7 per cent, $p < 0.05$) and five minutes after intubation (18 vs. −5 per cent, $p < 0.05$) (Figure 1). Heart rates five minutes after intubation were also significantly different between pancuronium and the pancuronium–metocurine groups (18 vs. 3 per cent, $p < 0.05$), since heart rate had returned close to baseline by this time in the pancuronium–meto-

TABLE II Haemodynamic measurements (mean ± SE) awake, after induction and after intubation in the four muscle relaxant groups. All patients were induced with high dose fentanyl.

	Baseline (awake)	*Induction 2 mins*	*Intubation 2 mins*	*Intubation 5 mins*
HR beats·min^{-1}				
V	69 ± 5	69 ± 5*	73 ± 6*	65 ± 6*
P	63 ± 5	77 ± 7	80 ± 7‡	74 ± 6
A	65 ± 4	66 ± 4*	79 ± 7	66 ± 5
PM	69 ± 6	76 ± 6	80 ± 6	71 ± 6*
MAP mmHg				
V	100 ± 3	103 ± 7	106 ± 6	104 ± 5
P	95 ± 5	95 ± 4	101 ± 5	96 ± 5
A	99 ± 3	92 ± 4	101 ± 4	99 ± 4
PM	93 ± 5	90 ± 8	93 ± 4	92 ± 4
PAD mmHg				
V	16 ± 3	17 ± 3	17 ± 3	17 ± 2
P	15 ± 2	16 ± 1	16 ± 1	15 ± 1
A	17 ± 2	19 ± 2	19 ± 2	19 ± 2
PM	15 ± 2	14 ± 2	15 ± 3	15 ± 2
CVP mmHg				
V	8 ± 1	10 ± 1	10 ± 1	9 ± 1
P	9 ± 1	8 ± 1	8 ± 1	7 ± 1
A	9 ± 1	12 ± 2	11 ± 1	11 ± 1
PM	9 ± 2	11 ± 1	10 ± 1	10 ± 1
CI L·min^{-1}·m^{-2}				
V	2.5 ± 0.1	2.5 ± 0.2	2.7 ± 0.2	2.5 ± 0.2
P	2.9 ± 0.3	3.0 ± 0.3	2.0 ± 0.4	2.9 ± 0.3
A	2.8 ± 0.3	3.0 ± 0.2	3.2 ± 0.3	2.9 ± 0.2
PM	2.7 ± 0.3	2.9 ± 0.3	2.9 ± 0.3	2.8 ± 0.2
SVR dynes·sec·cm^{-5}				
V	1534 ± 108	1569 ± 165	1550 ± 181	1627 ± 135
P	1261 ± 79	1257 ± 121	1354 ± 165	1350 ± 161
A	1461 ± 127	1136 ± 86†	1249 ± 112	1234 ± 93
PM	1389 ± 164	1194 ± 114	1284 ± 121	1292 ± 117

*$p < 0.05$ when compared to pancuronium as per cent change from baseline at the measurement time indicated.

†$p < 0.05$ when compared to vecuronium as per cent change from baseline after induction.

‡$p < 0.05$ when compared as per cent change from baseline for the same drug.

Abbreviations: V = vecuronium; A = atracurium; P = pancuronium; PM = pancuronium–metocurine mixture; HR = heart rate; MAP = mean arterial pressure; PAD = pulmonary artery diastolic pressure; CVP = central venous pressure; CI = cardiac index; SVR = systemic vascular resistance.

curine group, while it remained elevated in those who had received pancuronium. Other haemodynamic measurements after intubation were not significantly different between the study groups, or when compared to basal values within each group.

Changes in pulmonary artery diastolic and central venous pressures were not significantly different between the four study groups after induction or intubation (Table II). Pulmonary wedge pressure recordings showed individual variations and were technically unsatisfactory in four patients despite catheter manipulation. After excluding these patients, comparison of this measurement between study groups by analysis of variance for unequal numbers showed no significant differences.

Satisfactory muscle relaxation for intubation was

present in all patients. Fentanyl-induced rigidity was not observed. No adverse reactions occurred during the study; one patient who had received fentanyl–atracurium showed transient skin flushing. Continuous electrocardiographic monitoring showed no alterations in cardiac rhythm, ST segments or T waves. Arterial blood gases during mechanical ventilation were unremarkable.

Discussion

These results illustrate the different haemodynamic responses to neuromuscular blockers when used with high dose fentanyl in patients with coronary artery disease. Pancuronium, which has been recommended by some as the drug of choice for patients undergoing open heart surgery,[1,13] was compared with atracurium, vecuronium and a pancuronium–metocurine mixture. Doses in excess of ED_{95} were used to provide satisfactory neuromuscular blockade for endotracheal intubation. The potency of vecuronium is equal to or slightly greater than pancuronium (1–1.74:1), whereas atracurium is less potent than pancuronium (0.25–0.33:1).[4] During narcotic–nitrous oxide anaesthesia, vecuronium has been shown to be as potent as pancuronium in producing 95 per cent twitch depression;[5] hence, equal doses ($0.12\,mg \cdot kg^{-1}$) of pancuronium and vecuronium were chosen. A 1:4 ratio ($0.4 + 1.6\,mg \cdot ml^{-1}$) was used in the pancuronium–metocurine mixture as described by Lebowitz *et al.*[3] In our study, the contributions of preoperative medication and fentanyl to the observed haemodynamics cannot be distinguished from the cardiovascular effects of the neuromuscular blocker alone, as the latter was given during induction with fentanyl. However, since patient selection, preoperative medications, background anaesthesia (fentanyl dose), times of measurement were standardized, and since the four study groups were comparable regarding preoperative data (Table I) and baseline haemodynamics (Table II), differences in observed haemodynamic responses can be reasonably attributed to the different neuromuscular blockers used.

The most striking haemodynamic difference occurred in the HR response between the fentanyl–pancuronium and fentanyl–vecuronium groups, despite the same number of patients receiving chronic beta blocker therapy in both groups. This difference may be due to the fact that pancuronium, unlike vecuronium, has vagolytic effects on cardiac muscarinic receptors,[6] facilitates norepinephrine release,[7] and blocks norepinephrine reuptake by sympathetic nerve terminals.[8] The mean maximum HR observed with pancuronium in our patients was 80 beats/min (29 per cent increase over baseline), and this was not associated with alterations in rhythm or ECG signs of ischaemia. In contrast, Thomson and Putnins found that with ECG analysis using Holter monitor recordings new ECG ST-segment depressions occurred at HR increases between 28–57 per cent in 3/12 patients anaesthetized with fentanyl–pancuronium, leading the authors to recommend that pancuronium be best avoided in patients with coronary artery disease.[9] Consistent with the observation of Stoelting during halothane anaesthesia,[10] pancuronium caused no change in SVR with high-dose fentanyl anaesthesia.

Patients given vecuronium with high-dose fentanyl showed the greatest haemodynamic stability during induction and intubation, with minimal changes in HR, MAP, CVP, SVR and CI. This is consistent with previous reports that $0.28\,mg \cdot kg^{-1}$ vecuronium (12 times ED_{90}) with halothane anaesthesia in patients with coronary artery disease[11] and $0.3\,mg \cdot kg^{-1}$ vecuronium in healthy, anaesthetized patients[12] caused minimal cardiovascular effects.

A recent study by Salmenpera *et al.* comparing cardiovascular effects of pancuronium and vecuronium during high dose fentanyl anaesthesia showed different results to ours, because of a different experimental design. In that study, patients were given either vecuronium or pancuronium ten minutes after a fentanyl–succinylcholine induction. In this setting, pancuronium reversed the decreased HR and CI associated with fentanyl induction, whereas vecuronium caused further reductions in HR and CI. Thus, pancuronium, by its vagolytic effect, appeared to counteract the tendency of fentanyl to produce bradycardia, whereas the lack of cardiovascular effects associated with vecuronium appeared to be a disadvantage.[13] In our study, when pancuronium or vecuronium was given together with fentanyl, stable haemodynamics resulted with vecuronium; instead, it was the pancuronium–fentanyl combination that proved to be a disadvantage, producing increases in HR even in patients on chronic beta-blocker therapy. Increases in HR have also been described by Waller *et al.*, and Zurick *et al.* when high dose fentanyl and

pancuronium were given together at induction;[14,15] in the former study, the tachycardia was not associated with ECG signs of ischaemia.

Clinical use of combinations of metocurine and pancuronium arose from observations that potentiation of neuromuscular blockade with the mixture could allow lower doses of each drug for satisfactory muscle relaxation with attenuation of the autonomic and cardiovascular side effects of pancuronium.[3] Metocurine–pancuronium mixtures did result in significantly lesser tachycardia than pancuronium alone.[3] In our study, the mixture caused 12–19 per cent increases in HR after induction and intubation, which were less than those observed in the pancuronium group, and were not associated with ECG signs of ischaemia.

Atracurium has been reported to have minimal haemodynamic effects in both healthy patients[16] and those with coronary artery disease.[17] Although decreases in SVR with atracurium in our study caused mean arterial pressure to fall by only 7 mmHg, occasionally patients can unpredictably develop profound and rapid reductions in MAP and SVR, which may be related to histamine release.[17]

In summary, we showed that intubating doses of the neuromuscular blockers studied were relatively safe for use in patients with coronary artery disease when used with high dose fentanyl anaesthesia. Pancuronium was associated with greater increases in HR, while reductions in SVR occurred with atracurium. There were no clinically apparent adverse effects associated with these HR or SVR changes. The increased HR response could, however, be useful in the occasional heavily beta-blocked patient who comes to surgery with very slow heart rate. Pancuronium–metocurine mixtures caused a lesser tachycardia as compared to pancuronium. Vecuronium, which does not release histamine or show autonomic effects, was associated with the most stable overall haemodynamic course.

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Résumé

Afin de comparer les réponses hémodynamiques suite à l'administration de doses équipotentes de relaxants musculaires et de hautes doses de fentanyl (50 $\mu g \cdot kg^{-1}$), 40 patients normotendus sur béta-bloqueurs et bloqueurs de canaux calciques devant subir un pontage aorto-coronarien ont été randomisés en quatre groupes d'étude recevant les doses suivantes: 1) atracurium : 0.4 $mg \cdot kg^{-1}$, 2) pancuronium: 0.12 $mg \cdot kg^{-1}$, 3) vecuronium: 0.12 $mg \cdot kg^{-1}$, ou 4) pancuronium–metocurine (0.4 mg + 1.6 $mg \cdot kg^{-1}$) : 1 ml/10 kg. Les bloqueurs neuromusculaires ont été injectés avec le fentanyl lors de l'induction. La réponse hémodynamiques a été enregistrée quand les patients étaient conscients (contrôle), deux minutes après l'induction, et à deux et cinq minutes après l'intubation.

Le pancuronium a été le seul médicament associé à une augmentation significative de la fréquence cardiaque; aucun autre changement significatif n'est survenu pour aucun des groupes lorsque comparé à leurs données hémodynamiques de base respectivement. La fréquence cardiaque augmenta plus après induction au pancuronium comparativement à l'atracurium (23 vs 4 pour cent, $p < 0.05$), et au vecuronium (23 vs. 2 pour cent, $p < 0.05$), et comparativement au vécuronium après intubation (29 vs. 7 pour cent, $p < 0.05$). Le mélange pancuronium–métocurine provoqua une tachycardie qui était moindre mais non significativement différente lorsque comparé au pancuronium; cependant la fréquence cardiaque est retournée aux valeurs de contrôle en dedans de cinq minutes avec le mélange alors qu'elle resta élevée avec le pancuronium (3 vs. 18 pour cent, $p < 0.05$). La réistance vasculaire systémique diminua plus lors de l'induction avec l'atracurium comparativement au vecuronium (−18 vs. 1 pour cent $p < 0.05$). Ces changements dans la fréquence cardiaque ou la résistance vasculaire systémique n'était pas accompagnée de signe électrocardiographiques d'ischémie. Le vécuronium a permis une meilleure stabilité hémodynamique à tous les temps de mesure. En général, les doses d'intubation des relaxants musculaire étudiées apparaissent sécures lors de l'utilisation chez les patients avec maladie coronarienne artériosclérotique.