A comparison of pipecuronium with pancuronium on haemodynamic variables and plasma catecholamines in coronary artery bypass patients

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Pipecuronium bromide, a new neuromuscular relaxant with steroidal structure, is devoid of effects on the autonomic nervous system and may be useful in patients where haemodynamic stability is mandatory. However, tracheal intubation may alter this haemodynamic profile. Therefore, we carried out a prospective double-blind study in 30 patients undergoing coronary artery bypass surgery with the purpose (1) of determining if intubation influenced the haemodynamic stability in patients paralyzed with pipecuronium and (2) of comparing plasma catecholamine concentrations after pipecuronium with those after pancuronium. Thirty patients were randomized into two groups receiving either pipecuronium $100 \mu\text{g} \cdot \text{kg}^{-1}$ or pancuronium $150 \mu\text{g} \cdot \text{kg}^{-1}$ after induction of anaesthesia with midazolam and fentanyl. Haemodynamic variables and plasma catecholamines were measured before and after induction, after the muscle relaxant three times and twice after intubation. After anaesthesia induction decreases in heart rate (HR), mean arterial pressure (MAP) and cardiac index (CI) were observed in both groups. These haemodynamic variables were unchanged

after pipecuronium whereas after pancuronium HR increased from $53 \pm 11 \text{ b} \cdot \text{min}^{-1}$ to $64 \pm 9 \text{ b} \cdot \text{min}^{-1}$ after induction ($P < 0.05$) and CI from $2.5 \pm 0.5 \text{ L} \cdot \text{min}^{-1}$ to $3.0 \pm 0.8 \text{ L} \cdot \text{min}^{-1}$ ($P < 0.05$). Furthermore ECG signs of myocardial ischaemia appeared in four patients after pancuronium and the decay of plasma norepinephrine concentration was slower than with pipecuronium. We conclude that pipecuronium given after induction of anaesthesia is free of sympathomimetic or vagolytic activity and does not influence haemodynamic variables for up to ten minutes after tracheal intubation.

Key words

ANAESTHESIA: cardiac;

HEART: stimulation, ischaemia;

NEUROMUSCULAR RELAXANTS: pancuronium,
pipecuronium;

SYMPATHETIC NERVOUS SYSTEM: anaesthesia.

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Accepted for publication 21 January, 1994.

Le bromure de pipecuronium est un nouveau myorelaxant avec une structure stéroïdale similaire au bromure du pancuronium avec lequel il partage les propriétés pharmacocinétiques sans pour autant exercer un effet sur le système nerveux autonome. Cependant l'intubation endotrachéale effectuée après l'administration de ce myorelaxant pourrait changer son profil hémodynamique. C'est pourquoi nous avons effectué chez 30 patients devant subir une chirurgie coronarienne une étude prospective en double aveugle dans le but 1) d'investiguer si l'intubation endotrachéale change le profil hémodynamique chez le patient paralysé avec du pipecuronium et 2) de comparer les variations des taux plasmatiques des catécholamines après pipecuronium avec celles après pancuronium. Les patients sont randomisés en deux groupes selon le myorelaxant qui leur sera administré après l'induction anesthésique (midazolam-fentanyl) soit du pipecuronium $100 \mu\text{g} \cdot \text{kg}^{-1}$ soit du pancuronium $150 \mu\text{g} \cdot \text{kg}^{-1}$. Les variables hémodynamiques et les taux plasmatiques d'adrénaline et de noradrénaline sont mesurés une fois avant et une fois après l'induction, trois fois avant et deux fois après l'intubation. L'induction anesthésique provoque une diminution significative de la fréquence cardiaque (FC), de la pression artérielle moyenne et de l'index cardiaque (IC). Ces variables hémodynamiques restent inchangées après le pipecuronium

tandis que après le pancuronium une accélération de la FC de $53 \pm 11 \text{ b} \cdot \text{min}^{-1}$ à $64 \pm 9 \text{ b} \cdot \text{min}^{-1}$ ($P < 0.05$) concomitante avec une augmentation de l'IC de $2.5 \pm 0.5 \text{ L} \cdot \text{min}^{-1}$ à $3.0 \pm 0.8 \text{ L} \cdot \text{min}^{-1}$ ($P < 0.05$) sont observées. De plus, après l'administration de pancuronium on observe chez quatre patients des signes électrocardiographiques d'ischémie myocardique et le taux de norépinéphrine plasmatique diminue plus lentement qu'après le pipecuronium. En conclusion, nos résultats démontrent que le pipecuronium lorsqu'il est administré après l'induction anesthésique est exempt d'effets sympathomimétique ou vagolytique et ne modifie pas les variables hémodynamiques jusqu'à 10 min après l'induction.

The use of pancuronium for muscle relaxation during narcotic-based anaesthesia is popular because its vagolytic¹ and sympathomimetic^{2,3} properties tend to antagonize the untoward circulatory effects of opioids. However, in patients with coronary artery disease, a 25% incidence of myocardial ischaemia appeared on the electrocardiogram (ECG) during fentanyl-pancuronium induction of anaesthesia, which was higher than after other neuromuscular relaxants.⁴ Furthermore, these ECG changes were associated with an increase in heart rate of 28 to 57% above control, suggesting that pancuronium increased noradrenaline concentration at sympathetic nerve endings.

Pipecuronium bromide is structurally related to pancuronium⁵ and shares its neuromuscular effects and pharmacokinetic properties,⁶⁻⁸ however, it is devoid of effects on the autonomic nervous system.^{9,10} We confirmed these observations in a previous study comparing the cardiovascular effects of three different doses of pipecuronium (1, 2 and $3 \times \text{ED}_{95}$) with those of pancuronium ($2 \times \text{ED}_{95}$) in the anaesthetized non-stimulated and non-intubated patient.¹¹

However, the influence of pipecuronium on haemodynamic variables and on plasma catecholamine concentrations before and after tracheal intubation has not been reported.

We therefore designed a double-blind, randomized study in patients undergoing coronary artery surgery with the aims of: (1) determining the cardiovascular effects and the catecholamine responses of pipecuronium administered during induction of anaesthesia and after tracheal intubation and (2) of comparing these effects with those after pancuronium.

Methods

After approval of the protocol by the institutional review board for human studies, informed consent was obtained from 30 patients (ASA physical status III) scheduled for elective coronary artery bypass surgery (CABG). Exclu-

sion criteria were: emergency operation, unstable angina, left ventricular failure (clinical or proved at preoperative catheterisation), associated valvular heart disease, arterial hypertension, diabetes mellitus and liver or kidney disease. Patients whose preoperative ECG would have interfered with the interpretation of acute ST-segment changes during induction of anaesthesia and tracheal intubation, e.g., bundle branch block or left ventricular hypertrophy were also excluded. Preoperative beta-adrenergic and/or calcium channel blocker therapy was continued up to the morning of surgery.

Patients were randomly assigned to one of two treatment groups: (1) Group PIP ($n = 15$) received pipecuronium at a dose of $100 \mu\text{g} \cdot \text{kg}^{-1}$ ($=2 \times \text{ED}_{95}$) and (2) Group PAN ($n = 15$) received pancuronium at a dose of $150 \mu\text{g} \cdot \text{kg}^{-1}$ ($=2 \times \text{ED}_{95}$). Equipotent concentrations of the two muscle relaxants were prepared and delivered to the operating room in coded syringes.

Patients were premedicated with diazepam $0.15 \text{ mg} \cdot \text{kg}^{-1}$ *po* and morphine $0.10 \text{ mg} \cdot \text{kg}^{-1}$ *im* one hour before arrival in the anaesthesia induction room. In each patient a 20-gauge cannula was inserted into a radial artery and a triple lumen flow-directed pulmonary artery catheter in the pulmonary artery under local anaesthesia. Leads II and V₅ of the ECG were monitored continuously.

Anaesthesia was induced with midazolam $0.10 \text{ mg} \cdot \text{kg}^{-1}$ *iv* followed by fentanyl $0.015 \text{ mg} \cdot \text{kg}^{-1}$ *iv* given over two minutes. Three minutes later the muscle relaxant was administered, and ten minutes after its administration the tracheas were intubated, always by the same experienced anaesthetist. During induction, ventilation was manually assisted using 100% oxygen and after administration of the relaxant, was controlled by face mask to maintain normocarbida, as assessed in line by capnography (Datex Capnomac). Heart rate (HR), systolic, diastolic and mean radial artery blood pressure (SAP, DAP, MAP), central venous pressure (CVP) and systolic, diastolic and mean pulmonary artery pressure (SPAP, DPAP, MPAP) were monitored continuously. Pulmonary capillary wedge pressure (PCWP) was recorded and thermodilution cardiac output (CO) obtained in triplicate at each measurement time. Prior to each CO measurement, a calibrated ECG tracing of DII, V₁ and V₅ was obtained (Hewlett-Packard Page Writer II). All recordings were examined for changes of the ST-T segment by a cardiologist not involved in the study. Changes were defined as significant if: (1) there was a downsloping or horizontal depression of $>1 \text{ mm}$, or an upsloping of the ST segment $>2 \text{ mm}$ measured 0.06 sec from the J point or (2) the T-axis changed by $>30^\circ$.

Cardiac index (CI), stroke volume index (SVI), systemic and pulmonary vascular resistance indices (SVRI,

PRVI) and the rate pressure product ($RPP = HR \times$ systolic arterial pressure) were calculated by standard formulae.

At each measurement time 5–7 ml arterial blood were withdrawn from the radial artery cannula and put into precooled heparinized tubes. The tubes were cold centrifuged and the decanted plasma was stored in a freezer at -70°C . Analysis of plasma concentrations of epinephrine (E) and norepinephrine (NE) was performed by high-pressure liquid chromatography (HPLC),^{12,13} allowing detection of as few as $15 \text{ pg} \cdot \text{ml}^{-1}$ NE and $20 \text{ pg} \cdot \text{ml}^{-1}$ E per sample injected in the column with a coefficient of variation of 9% for E and 10.3% for NE between different samples and 7% for E and NE within the same sample.

Haemodynamic measurements, ECG recordings and arterial blood sampling were performed at the following times: t_{-10} : control before induction; t_0 : one minute after completion of induction; t_2, t_5, t_{10} : two, five and ten minutes after neuromuscular relaxant; t_{12}, t_{18} : two and eight minutes after tracheal intubation. The study ended with the last sampling of data seven to eight minutes after intubation.

All data are reported as mean $\pm$ SD. Differences between the various measurement times within one group were analyzed by ANOVA one-way analysis for repeated measures, followed by a Bonferroni test when the F-ratio resulted in a $P < 0.05$. Differences between the two groups at the same measurement time were analyzed by Student's *t* test for unpaired data. Chi-square analysis with Yates correction was used for proportions. A $P < 0.05$ was considered significant.

Results

As illustrated in Table I and Figure 1, demographic data and preinduction (t_{-10}) haemodynamic variables HR, MAP and CI were similar in both groups. Induction of anaesthesia with midazolam and fentanyl induced similar decreases of HR by 20%, of MAP by 30% and of CI by 20% in both groups ($P < 0.05$ compared with control at t_{-10}).

After pipecuronium HR, MAP and CI remained at postinduction values, whereas after pancuronium HR and CI returned to preinduction values ($P < 0.05$ compared with values at T_0).

The comparison between the two groups revealed that HR and MAP were higher in group PAN than in group PIP at t_2 and at all other measurement times following the administration of the muscle relaxants although the effect of pancuronium on MAP was very small. The difference in CI reached significance only at t_{10} , the last measurement before tracheal intubation. Changes in other haemodynamic variables were not significant and no dif-

TABLE I Preoperative demographic data (mean $\pm$ SD or number (*n*) of patients)

	PIP (<i>n</i> = 15)	PAN (<i>n</i> = 15)
Age (yr)	64 $\pm$ 7	60 $\pm$ 10
Sex (male/female) (<i>n</i>)	13/2	12/3
LVEF* (%)	50 $\pm$ 1	61 $\pm$ 8
Preoperative antianginal treatment† (<i>n</i>)	11	12
Beta-blocker (<i>n</i>)	3	2
Ca-channel antagonist (<i>n</i>)	4	5
Combined treatment (<i>n</i>)	4	5

*LVEF = left ventricular ejection fraction at preoperative catheterisation.

†Number of patients receiving beta-blocker, Ca-channel antagonists or both up to the morning of surgery.

FIGURE 1 Comparison of heart rate (HR), mean arterial pressure (MAP) and cardiac index (CI) between Group PAN (□ ... □) and group PIP (■ — ■); (for abbreviations of the measurement times cf. text).

☆ $P < 0.05$ compared with preinduction value.

★ $P < 0.05$ compared with postinduction value.

++ $P < 0.05$; ++ $P < 0.01$; comparison between groups.

TABLE II Synopsis of haemodynamic data

Haemodynamic variables (mean $\pm$ SD)	Neuro-muscular relaxant	Pre-induction (t_{-10})	1 min after induction (t_0)	2 min after induction (t_2)	5 min after induction (t_5)	10 min after induction (t_{10})	2 min after intubation (t_{12})	8 min after intubation (t_{18})
HR ($b \cdot min^{-1}$)	PAN	62 $\pm$ 11	53 $\pm$ 11 $\star$	64 $\pm$ 9 $\star$ ++	65 $\pm$ 10 $\star$ ++	64 $\pm$ 9 $\star$ ++	65 $\pm$ 10 $\star$ ++	65 $\pm$ 10 $\star$ ++
	PIP	65 $\pm$ 11	51 $\pm$ 11 $\star$	51 $\pm$ 10 $\star$	50 $\pm$ 9 $\star$	49 $\pm$ 9 $\star$	53 $\pm$ 10 $\star$	49 $\pm$ 9 $\star$
MAP (mmHg)	PAN	103 $\pm$ 18	77 $\pm$ 16 $\star$	78 $\pm$ 21 $\star$ +	83 $\pm$ 20 $\star$ +	86 $\pm$ 20 $\star$ +	94 $\pm$ 22 +	86 $\pm$ 21 $\star$ +
	PIP	99 $\pm$ 13	68 $\pm$ 17 $\star$	66 $\pm$ 14 $\star$	69 $\pm$ 14 $\star$	72 $\pm$ 14 $\star$	76 $\pm$ 13 $\star$	69 $\pm$ 13 $\star$
CI ($L \cdot min^{-1} \cdot m^{-2}$)	PAN	3.1 $\pm$ 0.5	2.5 $\pm$ 0.5	2.9 $\pm$ 0.8	3.0 $\pm$ 0.8 $\star$	3.0 $\pm$ 0.8 $\star$ +	3.1 $\pm$ 0.6 $\star$ ++	3.0 $\pm$ 0.6 $\star$ +
	PIP	3.1 $\pm$ 0.7	2.5 $\pm$ 0.6 $\star$	2.4 $\pm$ 0.6	2.3 $\pm$ 0.6	2.3 $\pm$ 0.6 $\star$	2.3 $\pm$ 0.5 $\star$	2.3 $\pm$ 0.4 $\star$
SVI ($ml \cdot m^{-2}$)	PAN	51 $\pm$ 7	49 $\pm$ 10	45 $\pm$ 11	46 $\pm$ 12	46 $\pm$ 10	48 $\pm$ 8	46 $\pm$ 8
	PIP	48 $\pm$ 11	50 $\pm$ 12	48 $\pm$ 12	46 $\pm$ 10	47 $\pm$ 16	45 $\pm$ 10	47 $\pm$ 9
CVP (mmHg)	PAN	8 $\pm$ 3	12 $\pm$ 5	9 $\pm$ 4	9 $\pm$ 3	9 $\pm$ 4	8 $\pm$ 3	8 $\pm$ 3
	PIP	9 $\pm$ 5	10 $\pm$ 4	10 $\pm$ 4	10 $\pm$ 4	10 $\pm$ 4	10 $\pm$ 4	10 $\pm$ 4
MPAP (mmHg)	PAN	22 $\pm$ 7	20 $\pm$ 3	20 $\pm$ 5	20 $\pm$ 4	20 $\pm$ 5	20 $\pm$ 6	20 $\pm$ 8
	PIP	24 $\pm$ 9	19 $\pm$ 6	19 $\pm$ 5	19 $\pm$ 5	19 $\pm$ 5	20 $\pm$ 6	18 $\pm$ 5
PCWP (mmHg)	PAN	14 $\pm$ 6	15 $\pm$ 4	12 $\pm$ 4	13 $\pm$ 4	13 $\pm$ 4	12 $\pm$ 4	11 $\pm$ 3
	PIP	14 $\pm$ 6	14 $\pm$ 5	13 $\pm$ 5	13 $\pm$ 4	14 $\pm$ 5	13 $\pm$ 4	13 $\pm$ 4

$\star P < 0.05$ compared with preinduction value.

$\star P < 0.05$ compared with postinduction value.

+ $P < 0.05$; ++ $P < 0.01$; comparison between groups.

HR = heart rate, MAP = mean arterial pressure, CI = cardiac index, SVI = stroke volume index, CVP = central venous pressure, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PAN = pancuronium, PIP = pipercuronium.

ferences between the two study groups were observed (Table II).

No differences were found between the two groups in the baseline (t_{-10}) E or NE concentrations. Compared with the value at $t_0 = 100\%$, plasma NE concentrations in group PIP decreased to $66 \pm 30\%$ before intubation ($P < 0.05$) and to $62 \pm 28\%$ thereafter (t_{12} and t_{18}) ($P < 0.05$). The corresponding values in group PAN were $83 \pm 34\%$ at t_{10} ($P < 0.05$) and $85 \pm 27\%$ at t_{12} and t_{18} ($P < 0.05$) respectively. Plasma NE concentrations were different between groups at three measurement times t_{10} , t_{12} and t_{18} ; no changes in plasma E levels were observed in either of the two groups (Figure 2).

Electrocardiographic abnormalities suggesting myocardial ischaemia after the administration of the neuromuscular relaxant were observed in 4/15 patients in Group PAN and none in Group PIP. However, for technical reasons, a complete set of ECG recordings could be obtained only in 12 patients in group PIP. The ECG-

changes in three of the four patients with myocardial ischaemia were not correlated with changes in haemodynamic variables, because HR and MAP did not differ from the mean values of the remaining patients without ECG-changes in group PAN. Only in the fourth patient did the HR increase from $60 b \cdot min^{-1}$ at t_0 to 82 and $86 b \cdot min^{-1}$ after pancuronium.

Discussion

The results of the present study demonstrate that pipercuronium and pancuronium administered in equipotent doses during induction of anaesthesia differ not only in their haemodynamic effects, but also in their catecholamine-responses: plasma NE concentrations during the induction of anaesthesia decreased more when using pipercuronium than pancuronium. Furthermore, our results confirm previous reports of a high incidence of ECG changes, suggesting myocardial ischaemia after pancuronium.⁴

FIGURE 2 Comparison of plasma norepinephrine (NE) and epinephrine (E) concentrations in Group PAN (□ ... □) and Group PIP (■ — ■). * $P < 0.05$ compared with postinduction value. + $P < 0.05$ comparison between groups.

In agreement with other studies, we demonstrated previously that pipecuronium, even when given in high doses ($3 \times \text{ED}_{95}$), is devoid of haemodynamic side effects.^{6,9,11} However, in that study¹¹ only small amounts of midazolam ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) and fentanyl ($5 \mu\text{g} \cdot \text{kg}^{-1}$) were used and the study ended before tracheal intubation. In the present study, extending beyond intubation, we used a higher dose of fentanyl to suppress the sympathomimetic stimulation induced by orotracheal intubation. Contrary to pancuronium, pipecuronium did not induce any changes in the haemodynamic variables measured, either before or after intubation. This observation suggests that pipecuronium has no sympathomimetic or vagolytic effects to oppose opioid-induced bradycardia or "amplify" the sympathomimetic response to intubation.^{14,15}

However, our investigation does confirm the results of previous studies, that the administration of a $2 \times \text{ED}_{95}$

dose pancuronium after induction of anaesthesia induces a sustained increase in HR and CI regardless of the induction agent used.¹⁶⁻¹⁹ This side effect of pancuronium may be attributed to its vagolytic¹ or sympathomimetic properties,^{2,3,20} the latter probably being the reason that in our study MAP was higher after pancuronium than after pipecuronium.

Venous plasma NE provides a useful estimation of sympathetic outflow²¹ and, therefore, the higher plasma NE concentration we observed ten minutes after pancuronium compared with pipecuronium is supporting evidence that the cardiovascular effects of pancuronium may be caused by increased sympathetic nervous activity resulting either from pre- or post-ganglionic facilitation of NE-release,^{22,23} or by inhibition of NE-uptake.²⁴ However, preoperative treatment with betablockers and calcium antagonists especially if given, as in our study, up to the morning of surgery, as well as the choice of anaesthetics used for premedication and induction of anaesthesia may have blunted the cardiovascular side effects of pancuronium²⁵ without affecting its impact on sympathetic neural activity; and this increased sympathetic activity may have favoured the appearance of myocardial ischaemia. Smaller doses of pancuronium,²⁶ or a specific sympatholytic medication may modify the influence of pancuronium on sympathetic neural activity, reducing the incidence of myocardial ischaemia.

In this context, pipecuronium appears to be a good alternative, because the comparison of $2 \times \text{ED}_{95}$ of pipecuronium with a similar dose of pancuronium clearly shows the advantage of pipecuronium over pancuronium with regard to haemodynamic stability and the incidence of myocardial ischaemia.

In conclusion, the cardiovascular and autonomic response to a given sequence of anaesthetic induction agents and tracheal intubation can be modified by the neuromuscular relaxant used. This observation may be important in patients with a compromised cardiovascular system.

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