

monitoring does not always ensure patient safety. Specifically, a disconnection in the airway circuit may not be detected by the low pressure alarm when using medium to high inspiratory flow rates in conjunction with a cascade humidifier or Portex Humid-Vent 1. The use of redundant monitors of ventilation such as an esophageal stethoscope might be advised to provide early warning of patient disconnection. Although disconnect alarms are important, they are not a substitute for vigilance on the part of the anesthesiologist.

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Cardiovascular Effects of Pipecuronium and Pancuronium in Patients Undergoing Coronary Artery Bypass Grafting

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Pipecuronium bromide (Arduan®) is a new, long-acting, nondepolarizing steroid muscle relaxant structurally related to pancuronium bromide.¹ The neuromuscular potency of pipecuronium compared to pancuronium is 1:1.5, respectively.² Its neuromuscular effects, as well as its pharmacokinetics, are similar to those of pancuronium.²⁻⁴

Studies in animals suggest that pipecuronium does not induce hemodynamic changes related to histamine release or to an effect on the autonomic nervous system.⁵ In early human studies with doses as great as $1.5 \times ED_{95}$, pipecuronium provided adequate muscle relaxation without significant hemodynamic effects,^{6,7} although some degree of bradycardia has occasionally been reported.⁸ Whether bradycardia is accentuated by large doses of pipecuronium and beta-adrenergic blocking drugs or calcium channel blocking drugs is not clear.

In contrast, pancuronium may produce tachycardia, even in patients treated with beta-adrenergic blocking

drugs,⁹ which may induce myocardial ischemia in patients with coronary-artery disease.¹⁰

The aim of the present study was to compare the cardiovascular effects of pipecuronium with those of pancuronium during induction of anesthesia with midazolam and fentanyl in patients undergoing coronary artery bypass grafting, and to determine whether or not pipecuronium causes bradycardia and hypotension.

MATERIALS AND METHODS

Informed consent was obtained from 30 ASA physical status 2 and 3 patients (mean \pm SD age and weight, 59 ± 9 yr, 75 ± 14 kg, respectively) about to undergo elective coronary artery bypass surgery. Local hospital committee approval was also obtained. Excluded from the study were patients with unstable angina, clinical signs of left ventricular failure, valvular heart disease, known arterial hypertension, and patients with liver or kidney disease.

The patients were randomly assigned to one of the four treatment groups. Group 1 ($n = 8$) received pancuronium at a dose of 0.15 mg/kg ($= ED_{95} \times 2$); groups 2 ($n = 6$), 3 ($n = 8$), and 4 ($n = 8$) received pipecuronium at doses of 0.05 mg/kg ($= ED_{95} \times 1$), 0.1 mg/kg ($= ED_{95} \times 2$), or 0.15 mg/kg ($= ED_{95} \times 3$), respectively.²

Preoperative beta-adrenergic blocking drug and calcium channel blocking drug therapy was continued until the morning of surgery. All patients were premedicated with morphine 0.1 mg/kg im and diazepam 0.15 mg/kg po 1 h prior to surgery. After arrival in the induction room, supplemental oxygen was administered through a face mask, ECG electrodes attached, and a peripheral ve-

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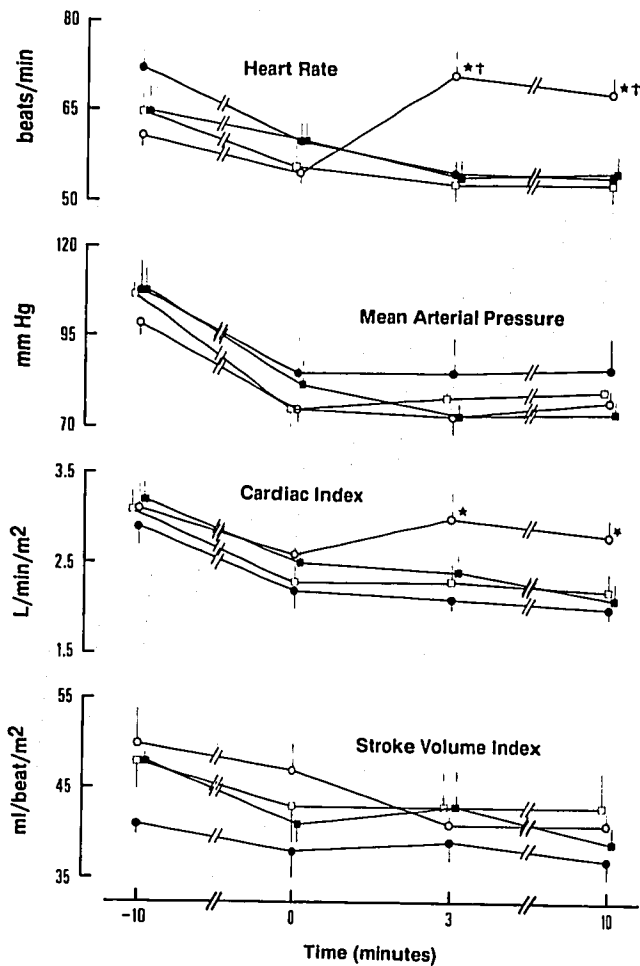


FIG. 1. Hemodynamic changes (mean \pm SEM) following anesthesia induction (time = 0) and muscle relaxant administration (time = 3 and 10 min) in the four patient groups. Symbols are: pancuronium ED₉₅ \times 2 \circ — \circ ; pipecuronium ED₉₅ \times 1 \bullet — \bullet ; pipecuronium ED₉₅ \times 2 \blacksquare — \blacksquare ; pipecuronium ED₉₅ \times 3 \square — \square . * P < 0.05, significantly different from pipecuronium. † P < 0.05, significantly different from before administration of muscle relaxant.

nous catheter, a central venous catheter, a pulmonary artery catheter (7F American Edwards Lab), and a radial artery catheter were inserted after local anesthesia.

Heart rate (HR), phasic and mean radial artery blood pressure (MAP), and phasic and mean pulmonary artery pressure (MPAP) were monitored continuously. Central venous pressure (CVP), pulmonary artery occlusion pressure (PCWP), and cardiac output were determined at each measurement time (see below). For pressure measurements, two calibrated quartz pressure transducers (1290 A, Hewlett Packard®) positioned at the mid-axillary line were used. Cardiac output was determined in triplicate by thermodilution at end expiration using an Edwards Computer 9520 A. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and

pulmonary vascular resistance index (PVRI) were calculated with standard formulae.

Five minutes after insertion of the various intravascular catheters, baseline (time = -10 min) hemodynamic data were measured, followed by induction of anesthesia. Anesthetic induction consisted of iv midazolam 0.10 mg/kg followed by 0.005 mg/kg of fentanyl. During the study period, ventilation was manually assisted to maintain normocarbica using 100% oxygen through a face mask. A second set of hemodynamic measurements was repeated when circulatory steady state was obtained following induction of anesthesia (time zero), after which the muscle relaxant was administered. Hemodynamic measurements were repeated 3 and 10 min after muscle relaxant administration, after which tracheal intubation was performed. At each measurement time, arterial blood samples were taken for blood gas analysis. A double blind protocol was applied, preparing and delivering the muscle relaxants in coded syringes each containing the same volume of solution. Muscle relaxants were injected as an iv bolus *via* the central catheter.

The data of the study were analyzed by means of the statistical program SPSSPC. For differences between the various measurement times within the same group, a one-way repeated measures ANOVA was performed followed by a modified paired Student's *t* test (Bonferroni's method) when the F-ratio resulted in a *P* value < 0.05. For differences between the four drug groups at the same measurement time, a one-way ANOVA was performed, followed by a Duncan's multiple comparison test when the F-ratio resulted in a *P* value < 0.05.

RESULTS

Hemodynamic variables are illustrated and compared in figure 1 and table 1. Initial hemodynamic variables were not significantly different in the four patient groups (at time -10 min). Significant changes following induction of anesthesia include a decreased HR in patients in group 2; decreased MAP in patients in groups 1, 3, and 4; and decrease in CI index in patients in groups 2, 3, and 4. However, there were no significant differences between the four groups following induction but before muscle relaxation (at time zero).

Following pancuronium administration, HR increased and was significantly different from before muscle relaxation at 3 and 10 min, and from before anesthesia at 3 min. There were no other changes of any hemodynamic variables due to the administration of either pancuronium or pipecuronium.

Statistical comparison between the four different treatment groups at 3 and 10 min following relaxation indicates that HR and CI were significantly increased in the patients receiving pancuronium compared to those receiving pi-

TABLE 1. Hemodynamic Variables

Variables	Groups	n	Time (Min)			
			-10	0	3	10
MPAP (mmHg)	1	8	19 ± 2	20 ± 1	18 ± 1	17 ± 1
	2	6	21 ± 3	17 ± 2	19 ± 1	19 ± 2
	3	8	20 ± 2	21 ± 2	20 ± 1	19 ± 2
	4	8	18 ± 2	20 ± 3	16 ± 1	15 ± 1
CVP (mmHg)	1	8	8 ± 1	11 ± 1	12 ± 1	8 ± 1
	2	6	8 ± 1	12 ± 2	12 ± 1	9 ± 1
	3	8	8 ± 2	12 ± 2	13 ± 2	12 ± 2
	4	8	6 ± 1	12 ± 3	10 ± 1	9 ± 1
PCWP (mmHg)	1	8	12 ± 2	14 ± 1	12 ± 1	11 ± 1
	2	6	13 ± 2	13 ± 2	12 ± 1	12 ± 2
	3	8	12 ± 2	13 ± 2	13 ± 2	12 ± 1
	4	8	12 ± 2	15 ± 2	10 ± 1	10 ± 1
SVRI (dynes · s ⁻¹ · cm ⁻⁵ · m ⁻²)	1	8	650 ± 126	610 ± 70	573 ± 82	617 ± 69
	2	6	623 ± 110	762 ± 75	513 ± 140	630 ± 110
	3	8	656 ± 77	653 ± 61	606 ± 79	616 ± 78
	4	8	574 ± 86	464 ± 108	493 ± 90	543 ± 124
PVRI (dynes · s ⁻¹ · cm ⁻⁵ · m ⁻²)	1	8	55 ± 10	56 ± 18	63 ± 15	65 ± 8
	2	6	75 ± 16	60 ± 12	58 ± 13	63 ± 19
	3	8	56 ± 12	79 ± 15	58 ± 9	70 ± 11
	4	8	52 ± 10	61 ± 15	66 ± 15	61 ± 8

Values are mean ± SEM. MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index.

pecuronium. No significant difference in any of the measured cardiovascular variables could be detected between patients in the three different pipecuronium groups.

DISCUSSION

Results of this study demonstrate that the hemodynamic variables were not altered following doses of pipecuronium as large as ED₉₅ × 3 in this patient population.

The lack of tachycardia following pipecuronium may offer an important advantage over pancuronium in patients with coronary artery disease. This advantage may, however, be negated if reports showing bradycardia following pipecuronium are confirmed. Wittek *et al.*⁸ have reported some degree of bradycardia following the administration of 1 × ED₉₅ of pipecuronium during halothane anesthesia in patients without coronary artery disease, but it was not possible from their study to distinguish between the effects of anesthesia or pipecuronium on the HR. This issue is of some importance inasmuch as the absence of cardiac stimulation by muscle relaxants may favor the development of bradycardia induced by anesthetic agents, similar to that reported following vecuronium.^{11,12}

During the present study, induction of anesthesia with midazolam and fentanyl was followed by decreased HR, MAP, and CI. Subsequent administration of pancuronium increased HR by 29% within 3 min, despite preoperative beta-adrenergic blocking drug treatment. The increased HR resulted in a higher CI in the patients receiving pan-

curonium, whereas no change in MAP was observed. It was noted that the peak of the HR increase occurred 3 min following the injection of pancuronium, and the HR stabilized after 10 min. After the administration of pipecuronium, there were not HR changes. For this reason, we have chosen the 3- and 10-min intervals for comparison of cardiovascular effects of pancuronium and pipecuronium.

We conclude that the administration of pipecuronium in a dose as large as 3 × ED₉₅ is accompanied by a hemodynamic stability, and represents a clinically useful alternative to pancuronium for muscle relaxation in patients with coronary artery disease in whom tachycardia is best avoided. In addition, the previously reported bradycardia attributed to this muscle relaxant could not be confirmed. The hazard of bradycardia and hypotension is not accentuated by the pre-treatment with beta-adrenergic blocker drugs and calcium-channel blocker drugs.

Results of this study are applicable only to patients receiving the particular induction sequence used in these patients. Patients receiving high-dose fentanyl, sufentanil, or alfentanil may develop bradycardia, because, similar to vecuronium, pipecuronium has no autonomic or vagolytic effects to oppose opiate-induced bradycardia.¹³

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