Pharmacokinetics and cardiovascular dynamics of pipecuronium bromide during coronary artery surgery

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The haemodynamic effects of 200 $\mu g \cdot kg^{-1}$ pipecuronium and pancuronium were compared under etomidate/piritramide anaesthesia in 20 patients scheduled for elective coronary artery surgery. Following the completion of the haemodynamic measurements (ten minutes), anaesthesia was maintained by etomidate/sufentanil infusion. The mean changes in cardiac output were approximately −19 and −2 per cent and in heart rate −1 and +26 per cent for pipecuronium and pancuronium respectively. Plasma and urine concentrations of pipecuronium were also measured and the pharmacokinetic variables obtained indicated rapid initial decrease in plasma concentration ($t_{\frac{1}{2}}$ = 7.6 minutes) followed by a longer terminal phase ($t_{\frac{1}{2}}$ = 161 minutes). The central compartment volume was 102 ± 24 $ml \cdot kg^{-1}$ and plasma clearance was 1.8 ± 0.4 $ml \cdot kg^{-1} min^{-1}$. Approximately 56 per cent of the dose was recovered from the urine within 24 hours of administration and about 25 per cent of this was the metabolite, 3-desacetyl pipecuronium. High-dose pipecuronium administration under the anaesthetic regimen employed did not produce deleterious haemodynamic effects. The pharmacokinetic variables after bolus injection of pipecuronium did not deviate from those reported under normothermic conditions.

Nous avons comparé les effets du pipécuronium et du pancuronium à raison de 200 $\mu g \cdot kg^{-1}$ sur l'hémodynamie de 20 sujets lors de leurs revascularisations coronariennes. Nous mesurions ces effets pendant une période de dix minutes sous anesthésie à l'étomidate et au piritramide, ce dernier étant ensuite remplacé par du sufentanil. Nous avons observé avec le pipécuronium et le pancuronium respectivement, des changements moyens de −19 et de −2 pour cent quant au débit cardiaque et de −1 et +26 pour cent quant au pouls. Par la mesure de ses concentrations plasmatiques et urinaires, nous avons pu établir que le pipécuronium encours une redistribution initiale rapide ($t_{\frac{1}{2}}$ = 7.6 min) suivie d'une élimination plus lente ($t_{\frac{1}{2}}$ = 161 min) avec un volume de distribution central estimé à 102 ± 24 $ml \cdot kg^{-1}$ et une clairance plasmatique de 1,8 ± 0,4 $ml \cdot kg^{-1} \cdot min^{-1}$. En moins de 24 heures, on a retrouvé dans les urines, près de 56 pour cent du pipécuronium injecté dont le quart sous forme de son métabolite, le 3-désacétyl pipécuronium. Avec le type d'anesthésie employé, l'injection à bonne dose de pipécuronium n'a donc pas entrainé d'effet hémodynamique néfaste. De plus, la cinétique d'un bolus de ce médicament s'est révélée semblable à celle observée en normothermie.

Key words

ANAESTHESIA: cardiovascular;
NEUROMUSCULAR RELAXANTS: pancuronium pipecuronium;
PHARMACODYNAMICS: pancuronium, pipecuronium;
PHARMACOKINETICS: pipecuronium;
SURGERY: cardiopulmonary bypass.

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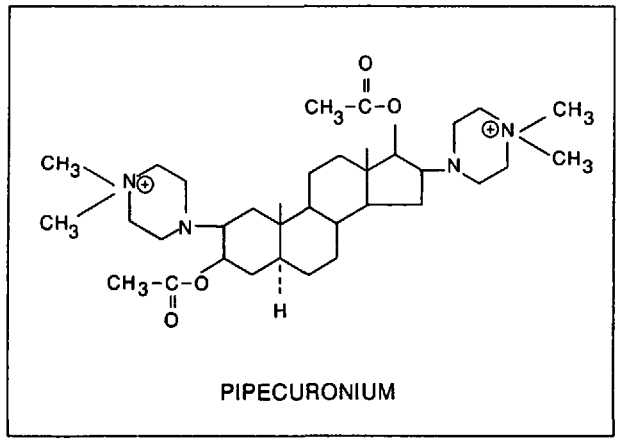
Pipecuronium bromide (2 beta, 16 beta-bis(4'-dimethyl-1'-piperazino)-3 alpha, 17 beta-diacetoxy- 5 alpha-androstane dibromide; Arduan®) is a steroidal neuromuscular blocking agent, resembling pancuronium bromide not only in its chemical structure (Figure 1), but also in the potency and time-course of its neuromuscular blocking effects.[1,2] The pharmacokinetic behaviour of this drug has been studied in animals[3–5] and in patients with normal and impaired renal function[6,7] although the study in humans by Tassonyi,[6] did not allow a proper pharmacokinetic analysis because of the limited duration of blood sampling. Earlier studies[1,3,9–13] both in animals and man have shown that the cardiovascular effects of this agent are minimal, lacking ganglion-blocking and/or histamine-releasing properties.[3] Pipecuronium does not affect myo-



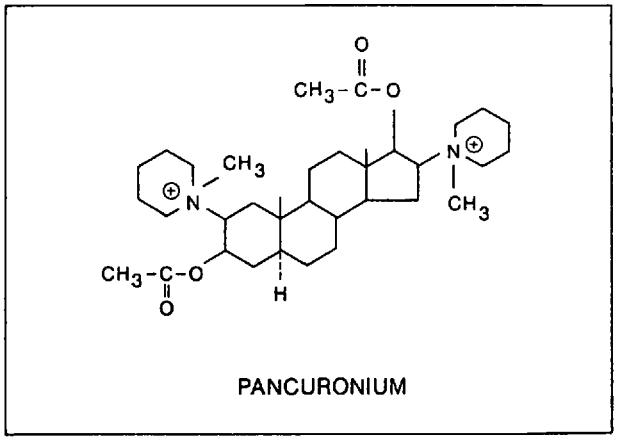


FIGURE 1 Structural formulas pipecuronium and pancuronium.

cardial blood supply or myocardial oxygen consumption in animals.[10] Barankay[14] suggested that, because of the absence of cardiovascular side-effects, it was a suitable agent for patients with severe cardiovascular disease. The present study was undertaken to investigate the haemodynamic effects and the pharmacokinetic disposition of a single bolus dose of pipecuronium, which was sufficient both for the conditions of the pharmacokinetic study and the duration of the surgical intervention.

Methods

Patients

The study was approved by the Ethical Committee of the University Hospital of Groningen. Twenty patients, scheduled for elective coronary artery surgery, ASA physical status class III, gave informed consent to participate in this study. Their age was between 21 and 65 yr, with a mean of 54 yr. Patients with a history of cardiac failure, valvular, or myocardial disease were excluded. In ten patients a dose of 200 $\mu g \cdot kg^{-1}$ (approximately four times the effective dose producing a neuromuscular blockade of 95 per cent) was administered, sufficient to cover the duration of surgery. The pharmacokinetic profile and cardiovascular responses to pipecuronium were studied. In order to compare the cardiovascular responses between both neuromuscular blocking agents, a matched control group (n = 10) received an equipotent dose of pancuronium (200 $\mu g \cdot kg^{-1}$).

Anaesthesia

Premedication consisted of butobarbitone, 100 mg orally on the evening before the operation and diazepam, 10–15 mg orally approximately 1.5 hr before the induction of anaesthesia. Cardiac maintenance medication was continued. After arrival in the operating room, peripheral venous, systemic arterial, central venous and pulmonary arterial (Swan-Ganz) lines were established under local anaesthesia. Following attachment of the monitoring devices a five minute-period was allowed for stablisation of the cardiovascular system and baseline measurements were obtained. Anaesthesia was induced with a bolus of piritramide 0.3 $mg \cdot kg^{-1}$, followed by an infusion of etomidate at a rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Once unconscious, the patients' lungs were ventilated with 100 per cent oxygen. End–tidal PCO_2 was kept between 3.5 and 4.5 kPa. When a stable level of anaesthesia had been achieved, 200 $\mu g \cdot kg^{-1}$ pipecuronium or pancuronium dissolved in 10 ml saline was injected IV over a ten seconds interval. Prior to administration (t = 0 mins) and for nine minutes thereafter haemodynamic measurements (Table II) were carried out continuously, with the exception of cardiac output measured by thermodilution and wedge pressure, which were estimated at three-minutes intervals.

This period was followed by tracheal intubation and the commencement of surgery. After the cardiovascular part of the study was completed anaesthesia was maintained with a continuous infusion of etomidate and sufentanil, according to the needs of the patient. The time elapsing between induction of anaesthesia and commencement of extracorporeal circulation averaged 105 min. The lowest temperature during surgery ranged from 28.8–25.6° C and the duration of bypass from 79 to 152 min (mean 109 min) respectively. Patients were rewarmed by extra corporeal circulation, usually until nasopharyngeal temperature had reached 37.5° C (ΔT 3–4° C). Thereafter central temperature again slowly decreased reaching a value at the end of the surgical procedure of approximately 35° C (ΔT 5–6° C).

All haemodynamic measurements were graphically displayed and stored in a Carola Database system developed in the department.[15] The measurements were used to calculate stroke volume index (SVI), left

ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), rate pressure product (RPP), triple index (TI), and left ventricular power (LV power). Statistical analysis was performed with the (un-)paired Student's t test and if necessary the Wilcoxon rank sum test. A value of $P < 0.05$ was considered to be significant.

Procedure of the kinetic study

Blood samples (8 ml) were collected via a central venous line. The first sample was taken before administration of pipecuronium, the others were collected 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360 and 480 min after the end of injection. Additional blood samples were taken five minutes after the start of extracorporeal circulation and immediately at the end of cardiopulmonary bypass. In order to prevent spontaneous degradation of pipecuronium, the samples were immediately acidified with 2 ml 1 M sodium di-hydrogen phosphate (NaH_2PO_4) solution to prevent spontaneous deacetylation. The plasma was separated by centrifuge and frozen, −18° C, to await analysis. Urine was collected over 24 hours and well mixed samples were taken from a previously inserted urethral catheter prior to and at 2, 4, 6, 8, 12, 18 and 24 hr after the administration of pipecuronium. Ten ml aliquots of the samples were frozen until analysis could be performed. Analysis was carried out by a fluorimetric method combined with thin-layer chromatography (TLC), based on the method described for pancuronium bromide.[16] The detection limit of pipecuronium in plasma and urine was 25 $ng \cdot ml^{-1}$. The standard deviation of pipecuronium fluorescence of plasma levels in the range from 25 $ng \cdot ml^{-1}$ to 1500 $ng \cdot ml^{-1}$ varied from 0.3 $ng \cdot ml^{-1}$ (11.9 per cent of mean) at the lower level and 35 $ng \cdot ml^{-1}$ (3.2 per cent of mean) at the higher level. The assay accuracy over the same range varied from 11.3 to 2.1 per cent.

Pharmacokinetic analysis was performed on the individual data by means of a computer program, based on iterative linear least-square regression analysis.[17] The volume of the central compartment (V_1), the apparent distribution volume ($V_{d\beta}$), the total plasma clearance (CL) and the area under the curve (AUC) were calculated, using the following equations:

$$[1] \quad V_1 = \frac{\text{Dose}}{C_1 + C_2}$$

$$[2] \quad V_{d\beta} = \frac{\text{Dose}}{AUC \cdot \lambda_2}$$

$$[3] \quad CL = \frac{\text{Dose}}{AUC}$$

$$[4] \quad AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$$

The values for renal clearance were calculated using the equation:

$$[5] \quad CL_R = \frac{A_{u(t_i - t_j)}}{AUC_{(t_i - t_j)}}$$

t_i and t_j indicate the time interval of urine collection. $A_{u(t_i - t_j)}$ is the renally excreted amount during the sampling period, and $AUC_{(t_i - t_j)}$ is the area under the plasma concentration decay curve between the two times and was calculated using the equation

$$[6] \quad AUC_{(t_i - t_j)} = \frac{C_1}{\lambda_1}(e^{-\lambda_1 t_i} - e^{-\lambda_1 t_j}) + \frac{C_2}{\lambda_2}(e^{-\lambda_2 t_i} - e^{-\lambda_2 t_j})$$

C_1 and C_2 are the concentrations at t = 0 obtained by extrapolation of the initial rapid and second slow component of the semilogarithmic plotted curves. λ_1 and λ_2 are the hybrid rate constants respectively.

Results

Haemodynamic study

The preoperative data of all 20 patients are summarized in Table I. There were no significant differences between the two groups in age, weight, basal heart rate (HR), systolic (SSAP) and diastolic (DSAP) systemic arterial pressures, left ventricular end-diastolic pressure (LVEDP) and New York Heart Association Class (NYHA). It should be noted that there were no females in the pipecuronium group, whereas in the pancuronium group four of the ten patients were females. Patients were not stratified regarding their preoperative cardiac medication, hence coexisting cardiac medication was variable between the two groups. Beta sympathetic blocking drugs were taken by five patients in the pipecuronium group and by eight patients in the pancuronium group. Comparable numbers with regard to calcium antagonists were seven and ten for patients in the pipecuronium and pancuronium groups respectively. The data from the haemodynamic measure-

TABLE I Preoperative characteristics and haemodynamic variables for both groups (mean (SEM))

		Pipecuronium (n = 10)	*Pancuronium (n = 10)*
Age	yr	53.5 (2.1)	58.7 (2.7)
Weight	kg	82.5 (2.8)	76.8 (2.8)
HR	bpm	68.0 (1.8)	69.0 (2.6)
SSAP	mmHg	146 (6.3)	143 (6.0)
DSAP	mmHg	87 (3.2)	81 (1.9)
LVEDP	mmHg	15.6 (2.6)	14.5 (1.7)
NYHA class	—	2.7 (0.2)	2.8 (0.1)

HR = heart rate, SSAP = systolic systemic arterial pressure, DSAP = diastolic systemic arterial pressure, LVEDP = left ventricular end-diastolic pressure.

TABLE II Haemodynamic measurements prior to (0 mins) and following an intravenous bolus dose of 200 $\mu g \cdot kg^{-1}$ pancuronium (pip) or 200 $\mu g \cdot kg^{-1}$ pancuronium (pan) (mean ± SEM)

	Time (mins)				
Variable	*0*	*3*	*6*	*9*	
HR bpm	58.5 ± 2.2	57.3 ± 3.6	56.7 ± 2.2	58.0 ± 2.2	pip
	58.5 ± 4.3	64.2 ± 4.9	69.9 ± 5.9	73.5 ± 8.2	pan
SSAP mmHg	124 ± 5.7	114 ± 4.7	107 ± 3.8	107 ± 3.2	pip
	128 ± 5.4	117 ± 7.6	115 ± 6.6	115 ± 6.6	pan
DSAP mmHg	69.5 ± 3.3	62.3 ± 3.5	61.3 ± 2.0	61.4 ± 2.3	pip
	65.0 ± 2.6	62.0 ± 5.4	60.0 ± 5.7	64.0 ± 5.1	pan
CVP mmHg	9.1 ± 1.3	7.7 ± 1.0	7.2 ± 1.2	6.6 ± 1.1	pip
	9.2 ± 0.9	7.8 ± 0.7	7.7 ± 0.7	8.2 ± 0.7	pan
SPAP mmHg	28.5 ± 1.9	25.6 ± 1.6	24.2 ± 1.4	23.5 ± 1.2	pip
	30.2 ± 2.7	28.1 ± 1.6	26.8 ± 1.8	27.8 ± 2.7	pan
DPAP mmHg	12.4 ± 1.6	11.2 ± 1.6	10.0 ± 1.2	10.5 ± 1.4	pip
	12.8 ± 1.1	10.7 ± 1.3	10.1 ± 1.4	10.9 ± 1.9	pan
PCWP mmHg	12.5 ± 1.2	10.5 ± 1.3	10.1 ± 1.1	9.4 ± 1.1	pip
	12.2 ± 0.6	11.2 ± 0.9	10.0 ± 1.2	11.1 ± 1.3	pan
CO l min^{-1}	4.7 ± 0.4	4.1 ± 0.3	4.1 ± 0.2	3.8 ± 0.3	pip
	5.5 ± 0.7	5.1 ± 0.7	5.4 ± 1.6	5.4 ± 0.7	pan

HR = heart rate, SSAP = systolic systemic arterial pressure, DSAP = diastolic systemic arterial pressure, CVP = central venous pressure, SPAP = systolic pulmonary arterial pressure, DPAP = diastolic pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure, CO = cardiac output.

TABLE III Haemodynamic values [mean (SEM)] after induction of anaesthesia, just before and 9 min after the administration of pipecuronium (200 $\mu g \cdot kg^{-1}$) or pancuronium (200 $\mu g \cdot kg^{-1}$) in patients scheduled for CA surgery

	Pipecuronium		*Pancuronium*	
Haemodynamic variables	*0 min*	*9 min*	*0 min*	*9 min*
HR min^{-1}	58.5 (2.2)	58 (2.2)	58.5 (4.3)	73.5 (8.2)†*
SSAP mmHg	124 (5.7)	107 (3.2)†	128 (5.4)	115 (6.6)†
DSAP mmHg	69 (3.3)	61 (2.3)†	65 (2.6)	64 (5.1)
CVP mmHg	9.1 (1.3)	6.6 (1.1)†	9.2 (0.9)	8.2 (0.7)
SPAP mmHg	29 (1.9)	24 (1.2)†	30 (2.7)	28 (2.7)
DPAP mmHg	12 (1.6)	11 (1.4)	13 (1.1)	11 (1.9)
PCWP mmHg	13 (1.2)	9 (1.1)†	12 (0.6)	11 (1.3)
CPP mmHg	57 (2.3)	52 (1.7)	53 (1.6)	53 (3.2)
CO l min^{-1}	4.7 (0.4)	3.8 (0.3)†	5.5 (0.7)	5.4 (0.7)*
SVI $ml \cdot m^{-2}$	42 (3.2)	35 (3.1)	50 (5.1)	40 (3.6)
SVR $dyn \cdot s \cdot cm^{-5}$	1444 (152)	1542 (128)	1231 (114)	1192 (143)*
RPP mmHg $min^{-1} \cdot 10^{-3}$	7.3 (0.5)	6.2 (0.4)†	7.6 (0.8)	8.8 (1.6)*
TI $mmHg^2\ min^{-1} \cdot 10^{-3}$	94 (12.3)	60 (8.5)	92 (10.2)	114 (32.5)*
LVSWI nm^{-2}	43 (4.6)	32 (3.0)†	50 (5.9)	37 (3.1)†
LV power	0.8 (0.01)	0.6 (0.01)†	0.95 (0.02)	0.9 (0.02)*

HR = heart rate, SSAP = systolic systemic arterial pressure, DSAP = diastolic systemic arterial pressure, CVP = central venous pressure, SPAP = systolic pulmonary arterial pressure, DPAP = diastolic pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure, CPP = coronary perfusion pressure, CO = cardiac output, SVI = stroke volume index, SVR = systemic vascular resistance, RPP = rate pressure product, TI = triple index, LVSWI = left ventricular stroke work index, LV power = left ventricular power.
Statistical significance:
*unpaired t test/Wilcoxon test. $P < 0.05$. Inter-group at 0 and 9 minutes.
†paired t test. $P < 0.05$. Intra-group between 0 and 9 minutes.

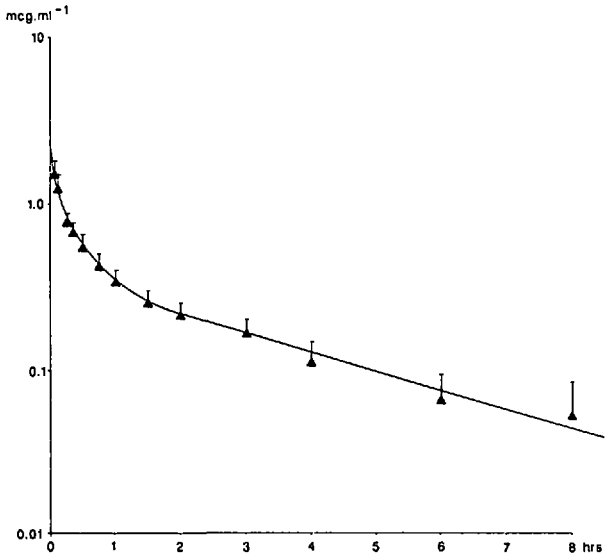


FIGURE 2 Mean plasma concentration decay curve of pipecuronium following a dose of 200 $\mu g \cdot kg^{-1}$ intravenously (mean ± SD).

ments are shown in Table II. Table III compares the mean values in and among the two groups, calculated from the measurements prior to the administration of the neuromuscular blocking agents (0 mins) and those obtained at nine minutes after injection. In most patients in the pancuronium group a moderate but consistent increase in heart rate was measured. However, two patients developed a more pronounced tachycardia. In addition to the increase in heart rate there was a significant decrease in the systemic systolic arterial pressure and in the left ventricular stroke work index. However, in the pipecuronium group a greater number of significant changes were observed. The SSAP, DSAP, CVP, SPAP, and the PCWP decreased significantly during the measuring period. The values for cardiac output, RPP, LVSWI, and LV power decreased simultaneously. Heart rate did not change with time and was not influenced by the presence or absence of beta-adrenergic blocking agents. Comparison between the two groups shows no significant differences in the measured and calculated values at zero minutes. However, at nine minutes, patients in the pancuronium group had a significantly higher heart rate and cardiac output. Derived values such as RPP, TI and LV power were also significantly higher in the pancuronium treated group.

Pharmacokinetic study

The mean plasma concentration decay curve of pipecuronium, following an intravenous dose of 200 $\mu g \cdot kg^{-1}$, is shown in Figure 2. The derived variables are listed in Table IV. The cumulative urinary excretion of pipecuronium and the only metabolite (3-desacetyl pipecuronium) found so far are shown in Figure 3. The potential 17-OH and the 3,17-diOH metabolites could neither be demonstrated in plasma nor in urine. The 3-OH metabolite also did not reach detectable plasma levels using the present

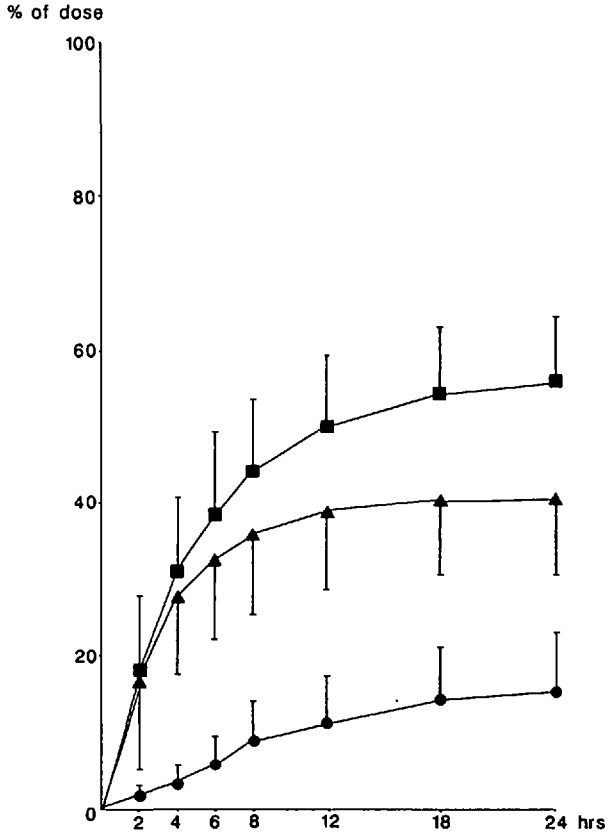


FIGURE 3 Mean cumulative urinary excretion of pipecuronium (▲), 3-desacetyl pipecuronium (●), and the total (■) urinary excretion. The vertical bars indicate the standard deviation (n = 10).

TABLE IV Pharmacokinetic variables of pipecuronium bromide following an intravenous bolus dose of 200 $\mu g \cdot kg^{-1}$ in patients undergoing coronary artery surgery (mean ± SD)

Variables	*Units*	
C_1	$\mu g \cdot ml^{-1}$	1.58 ± 0.47
C_2	$\mu g \cdot ml^{-1}$	0.406 ± 0.106
$t_{\frac{1}{2}}$ alpha	min	7.6
$t_{\frac{1}{2}}$ beta	min	161
$Lambda_1$	min^{-1}	0.0907 ± 0.0280
$Lambda_2$	min^{-1}	0.0043 ± 0.0009
V_1	$ml \cdot kg^{-1}$	102 ± 24
V_{db}	$ml \cdot kg^{-1}$	353 ± 83
CL	$ml \cdot kg^{-1} \cdot min^{-1}$	1.8 ± 0.4
AUC	$\mu g \cdot min \cdot ml^{-1}$	110 ± 25

The half-lives were calculated using t = ln 2/lambda.

TABLE V Renal clearance at various time intervals after the administration of pipecuronium bromide (mean ± SD)

Time after pipecuronium administration (hour)		
t_i	t_j	*Renal clearance* ($ml \cdot kg^{-1} \cdot min^{-1}$)
0	2	0.71 ± 0.46
2	4	1.29 ± 0.72*
4	6	1.19 ± 0.54*
6	8	1.62 ± 0.74

All values, except those marked with an asterisk, differed significantly between each other ($P < 0.05$). Statistics were carried out using the paired t test. See for interpretation of t_i and t_j the text.

method, but could be clearly identified in the urine. The renal clearance (CL_R), estimated from the two hourly collected urine samples is listed in Table V. Renal clearance was not constant in time, but increased showing its highest value six to eight hours after the administration of pipecuronium. The mean renal clearance calculated over 24 hours was 0.98 $ml \cdot kg^{-1}min^{-1}$. The non-cumulative urinary excretion of pipecuronium and 3-desacetyl pipecuronium are shown in Figure 4.

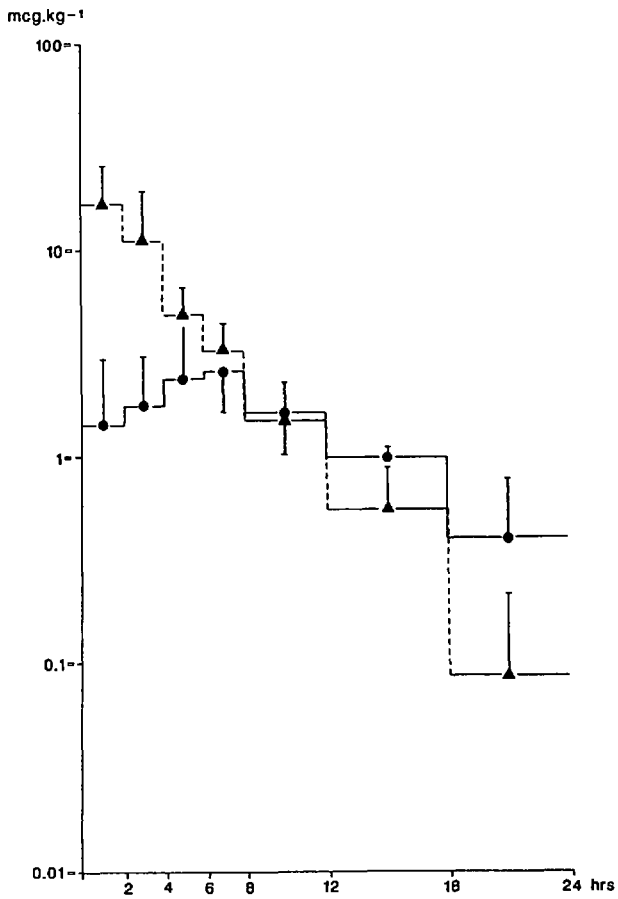


FIGURE 4 Mean urinary excretion rates of pipecuronium (▲) and 3-desacetyl pipecuronium (●) indicated as $\mu g \cdot kg^{-1}$, per urinary fraction. The vertical bars indicate the standard deviation (n = 10).

Discussion

The haemodynamic study

The present and previous studies[19-21] demonstrate that pancuronium produces, in most instances, a moderate increase in heart rate, presumably due to its vagolytic activity. This increase may, in part, counteract the haemodynamic effects of anaesthesia and result in a less pronounced decrease in cardiac output and blood pressure. The increase in heart rate was reported to be unrelated to dose, unpredictable[22] and closely related to a higher incidence of myocardial ischaemia.[23] It could be more than a coincidence that only the two patients in the pancuronium group, who did not receive beta blocking drugs, developed a more pronounced increase in heart rate. It has been clearly demonstrated by Karliczek *et al.*[18] that general anaesthesia ia a powerful modulator of the autonomic balance. Heinonen *et al.*[24] have shown a higher incidence of haemodynamic effects when pancuronium was supplemented by high-dose fentanyl anaesthesia, than in this study. These observations support the contention that the frequency and severity of the haemodynamic effects of neuromuscular blocking agents may be modulated by the technique and the depth of anaesthesia. The etomidate/piritramide infusion technique was selected for general anaesthesia because of its haemodynamic stability, compared with anaesthesia techniques when used in combination with pancuronium.[18] This has been a consistent observation in studies in both animals and man.[10,14] Unlike pancuronium, pipecuronium fails to counteract the negative chronotropic effect of opiate anaesthesia.[3] Pipecuronium bromide in a bolus dose of 200 $\mu g \cdot kg^{-1}$ did not produce tachycardia. Although vagolytic drugs were absent, neither unacceptably low heart rates nor ventricular escape beats were registered. Although significant decreases in systemic arterial systolic, diastolic and central venous and pulmonary capillary wedge pressures occurred with a concomitant significant decrease in cardiac output, these were associated with a relatively stable systemic vascular resistance together with significant reductions in rate pressure product, triple index and left ventricular power. In the present study one of the important effects of pipecuronium was the decrease in left ventricular power (decrease by 25 per cent; Table III), which parallelled the changes in the systemic arterial pressure. The resulting decrease in coronary perfusion pressure could result in a

diminished oxygen delivery to the cardiac muscle. Sonntag,[25] however has emphasized that diminished oxygen delivery following a decrease in arterial blood pressure might be compensated by an even more pronounced reduction in oxygen demand, which occurs due to a decrease in cardiac work. In the present study an additional slight decrease in diastolic arterial pressure with an unaltered diastolic time interval seemingly benefited the oxygen delivery/demand ratio in the pipecuronium-treated patients. The unchanged systemic vascular resistance after pipecuronium administration suggests that an indirect (alpha adrenergic blocking) or direct effect upon smooth muscle tone of blood vessels is unlikely in the clinical dose range. The improvement of the oxygen delivery/demand ratio, associated with the use of pipecuronium in this particular anaesthetic technique, may be of benefit for patients with ischaemic heart disease. The lack of cardiovascular effects with pipecuronium may unmask the negative inotropic and chronotropic effects due to induction of anaesthesia.

The pharmacokinetic study

The plasma concentration decay curve of pipecuronium following a bolus dose of 200 $\mu g \cdot kg^{-1}$ is best described by a continuously declining bi-exponential curve. Caldwell *et al.*[28] studied the pharmacokinetics of pipecuronium (70 $\mu g \cdot kg^{-1}$) in patients, anaesthetized with halothane and nitrous oxide. The apparent distribution volume in our study ($V_{d\beta} = 353 \pm 83$ ml$\cdot kg^{-1}$) was of the same order of magnitude as that reported by Caldwell ($V_{dss} = 309 \pm 103$ ml$\cdot kg^{-1}$) and the total plasma clearance of 1.8 ± 0.4 ml$\cdot kg^{-1} \cdot min^{-1}$ was almost identical to the value reported by Caldwell (2.4 ± 0.6 ml$\cdot kg^{-1} \cdot min^{-1}$). The estimated half-life of pipecuronium during cardiopulmonary bypass approximated 157 min and did not differ significantly from the terminal half-life in this study (161 mins) or from the value reported by Caldwell (137 mins). The overall effect of hypothermia and bypass did not appear to influence the terminal half-life of pipecuronium when given in this dosage regime.

It has been reported that renal elimination of neuromuscular blocking agents decreases during hypothermia.[26–29] In the present study the renal clearance of pipecuronium increased with time (see Table V). An explanation for this phenomenon could probably be diminished renal perfusion due to the relatively hypovolaemic preoperative state of our patients (high haematocrit value) in combination with the depressant effect on the cardiac output, caused by the induction of anaesthesia. We suggest that renal clearance most probably increases due to the haemodilution and improvement of the renal circulation during extra corporeal circulation. Rewarming the patient to normal body temperature (6–8 hr after induction of anaesthesia) led to a further improvement of renal clearance. The mean renal clearance over 24 hr was 0.98 ml$\cdot kg^{-1} \cdot min^{-1}$ and the total plasma clearance amounted to 1.8 ml$\cdot kg^{-1} \cdot min^{-1}$ (Table IV). The ratio of the renal to total plasma clearance, therefore, is 0.54. This is similar to the fraction of the administered dose of pipecuronium excreted in the urine (0.56, see Figure 3) over the same time interval.

The plasma concentration decay of pipecuronium was observed for an eight-hour period (Figure 2). Calculating the mean renal clearance, using equation [5], means an extrapolation of the plasma concentration decay curve to 24 hr. The calculated ratio of 0.54, using this equation [5], equals the measured fraction of the administered dose of pipecuronium, excreted in 24 hours in the urine. Therefore we conclude that the renal clearance, calculated by extrapolation of the plasma curve, appears to be reliable and the pharmacokinetic variables calculated over an eight-hour period and used to describe the plasma concentration decay curve are acceptable.

The percentage of pipecuronium excreted unchanged in the urine over 24 hr accounted for 41 per cent of the administered dose (see Figure 3). This supports the observation that renal excretion contributes in a major degree to the total elimination of pipecuronium both in animal and in man. The question arises which mechanism(s) counteract(s) the effect of the increase in renal clearance in the course of the experiment, for total plasma clearance appeared to be constant. A progressive diminution in liver function and a subsequent decrease in hepatic storage, due to the hypothermic bypass, may be responsible for the obligatory reduction in non-renal clearance with time. Further investigations are necessary to elucidate the underlying mechanism(s) to this reciprocity of non-renal and renal clearance. In this study we found that 15 per cent of the administered dose of pipecuronium was excreted in the urine as 3-desacetoxy pipecuronium (see Figure 3). This is approximately one-fourth of the total renal excretion. Yet, we could not detect the 3-OH metabolite in plasma. The formation of the 3-OH metabolite from its parent compound was probably not constant in time as changes in temperature during cardiopulmonary bypass can alter the rate of metabolism.[30] Because renal elimination was not constant and determination of the low plasma concentrations of 3-desacetyl pipecuronium was not possible, further analysis of urinary data was not feasible. Obviously, a more sensitive analytical technique is needed to elucidate the pharmacokinetic behaviour of 3-desacetoxy pipecuronium.

Conclusions

In the present study pipecuronium appeared to be a useful neuromuscular blocking agent for patients undergoing

hypothermic coronary bypass surgery. The cardiovascular side-effects were potentially less deleterious than those of pancuronium, particularly with respect to heart rate. The pharmacokinetic profile of pipecuronium, given in a bolus dose of 200 $\mu g \cdot kg^{-1}$ at induction of anaesthesia, appears to be similar to that observed after lower doses of pipecuronium in studies without hypothermic bypass. Pipecuronium seems to be a useful addition to drugs available for patients with heart disease, undergoing prolonged surgery.

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