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Effect of Pancuronium on Plasma Free-Norepinephrine and Epinephrine in Adult Cardiac Surgical Patients

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Since diazepam-ketamine induction sequences *in healthy humans* cause no significant increase in plasma free-norepinephrine and epinephrine, blood pressure and heart rate, we have frequently used a diazepam-ketamine pancuronium sequence for induction of anesthesia in patients undergoing open-heart surgery. In order to assess objectively the influence of pancuronium on sympathetic activity in cardiac patients, plasma free-norepinephrine and free-epinephrine were measured by Vendsalu's method in the arterial blood of 12 patients who were to undergo valve replacement or coronary bypass. At the same time, arterial pressure measured by a strain-gauge from the radial artery and heart rate measured by ECG were continuously recorded during induction with diazepam 0.3 mg/kg, followed 10 min later by ketamine 2.0 mg/kg. No significant changes occurred in these parameters before pancuronium administration. Plasma free-norepinephrine and free-epinephrine concentrations before and 5 min after pancuronium 0.1 mg/kg given over a 1-min period were 0.42 ± 0.05 (mean $\pm$ s.e.mean) and 0.45 ± 0.05 ng/ml ($P > 0.1$) and 0.01 ± 0.003 and 0.02 ± 0.009 ng/ml ($P > 0.1$), respectively. A significant increase in heart rate followed pancuronium administration from 75.0 ± 4.0 to 90.0 ± 6.0 beats/min ($P \leq 0.001$). The corresponding systolic and diastolic direct arterial pressures were $148.0 \pm 9.4/74.0 \pm 6.0$ and $153.0 \pm 8.3/81.0 \pm 5.2$ mmHg ($P > 0.05$). Although a statistically significant increase in heart rate was observed after pancuronium, no significant increase was found in plasma free-norepinephrine, epinephrine or direct arterial pressure.

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Tachycardia following pancuronium in conscious and anesthetized man has been reported by several authors (FOLDES et al. 1971, KELMAN & KENNEDY 1971, STOELTING 1972) and has been explained on the basis of a specific, competitive blockade of cardiac muscarinic receptors in dogs (SAXENA & BONTA 1971) and by increased sympathetic outflow as evidenced by increased plasma norepinephrine concentration, following its administration in man (NANA et al. 1973). Recently, DOMENECH et al. (1976) have suggested that pancuronium increases norepinephrine release from the postganglionic adrenergic nerve endings in dogs.

Since we have used pancuronium in cardiac patients for several years without incident, we were interested in finding out if it does indeed cause sympathetic stimulation, as reflected in circulatory changes accompanied by increased plasma free-norepinephrine and epinephrine concentrations. The study by NANA et al. (1973) claiming increased catecholamine levels caused by pancuronium did not have a homogenous group of patients, lacked a standardized protocol for administration of anesthesia, and did not provide for eliminating the effect of positioning, endotracheal intubation and surgical stimulation prior to blood sampling. The present study was, therefore, designed to control all the known variables that may influence sympa-

thetic activity, so that any observed changes following pancuronium could be ascribed to this drug alone.

MATERIALS AND METHODS

Twelve adult patients who were scheduled for open-heart surgery for valvular replacement (n=8) and direct aorto-coronary saphenous vein bypass operations (n=4) were studied. They had not had cortisol therapy, propranolol and/or drugs which might alter autonomic tone. The mean age of the patients was 53.0 y (range 29–65 y), mean weight 67.0 kg (40–95 kg), and mean height 166 cm (150–182 cm).

Preanesthetic medication consisted of 0.15 mg/kg diazepam and 0.15 mg/kg morphine sulfate. Atropine was not used in the premedication and/or prior to the study. None of the patients were sprayed with a local anesthetic prior to or during the study. No skin preparation, instrumentation (e.g., bladder catheterization, CVP–catheter placement), or positional changes were allowed before and/or during the study. There was a period of 5–10 min between the insertion of an arterial plastic catheter and the first arterial baseline blood sampling.

Anesthetic induction was accomplished by the administration of 0.3 mg/kg diazepam intravenously over 2 min while the patient spontaneously breathed 100% oxygen to avoid arterial hypoxemia. Ten minutes after diazepam, 2.0 mg/kg ketamine hydrochloride was given over a 1-min period into the peripheral intravenous line. After an additional 5-min waiting period, 0.1 mg/kg pancuronium was given intravenously over a 1-min period. Timing began at the end of the injection. Throughout the study, ventilation was manually assisted in order to maintain Pa_{CO_2} between 35–45 mmHg and to avoid reduction in Pa_{O_2} below 90 mmHg. Arterial blood gases were monitored frequently throughout the study.

The plasma free-norepinephrine and epinephrine were determined in duplicate from the arterial samples taken before induction and 15 min after induction but before pancuronium, and 5 min after pancuronium but prior to intubation by Vendsalu's method as modified by Kelsch et al. (1971). Laboratory personnel were not aware of the time of sampling, nor of the sequence of samples or the nature of the study.

Arterial blood pressure was recorded on a Hewlett Packard multichannel recorder via a Hewlett Packard strain-gauge connected to an indwelling catheter in the radial artery. ECG lead II or the lead giving the tallest R-wave was continuously recorded and utilized in the calculation of heart rate at the time of sampling.

Patients #6 and #10 received continuous i.v. infusions of sodium nitroprusside throughout the study.

The paired *t*-test was used for statistical evaluation of the data, a P value of <0.05 being considered statistically significant.

RESULTS

(1) *Plasma free-norepinephrine and epinephrine*: No significant increase in mean plasma free-norepinephrine concentrations was observed following induction and following pancuronium in the 12 patients, as seen in Table 1. Mean plasma free-epinephrine concentration decreased significantly following induction of anesthesia with diazepam and ketamine and showed no further significant change following pancuronium administration. A marked increase in norepinephrine and epinephrine concentrations occurred only in patient #2 with marked Pa_{CO_2} elevation. Elimination of patient #2 from the statistical evaluation of norepinephrine and epinephrine concentrations resulted in no change in statistical significance, although both mean values were reduced following pancuronium administration.

(2) *Heart rate*: A significant increase ($P<0.001$) in heart rate occurred following pancuronium administration, as indicated in Table 2. The marked increase in heart rate in patients #2, 6 and 8, accounting for 153%, 128%, and 121%, respectively, of the baseline value, resulted in a large standard deviation. Elimination of patients #2, 6 and 8, however, did not alter the statistical significance. The mean increase in the remaining patients (n=9) was 13% of the baseline heart rate, as compared to a mean of 19% for the entire group of 12 patients. No reduction in heart rate was observed in any of the patients after pancuronium administration.

(3) *Direct arterial pressure*: Diastolic blood pressure readings were significantly increased ($P<0.05$) following diazepam-ketamine induction over baseline values, while systolic pressure readings did not show any significant change. Systolic and diastolic pressure readings following pancuronium were not significantly different from corresponding values ($P>0.05$) prior to its administration. Deletion of patients #6 and 10, who received sodium nitroprusside throughout the study, did not

Table 1

Plasma free-norepinephrine and free-epinephrine concentrations following diazepam-ketamine-pancuronium in cardiac patients.

No.	Age (y)	Sex	Weight (kg)	Norepinephrine conc. ng/ml			Epinephrine conc. ng/ml		
				Baseline	After diazepam-ketamine	After pancuronium	Baseline	After diazepam-ketamine	After pancuronium
1	55.0	F	62.0	0.30	0.36	0.38	0.15	0.00	0.00
2*	60.0	F	46.0	0.50	0.48	0.67	0.20	0.05	0.10
3	55.0	M	58.0	0.47	0.85	0.92	0.00	0.00	0.00
4	29.0	F	50.0	0.30	0.38	0.45	0.00	0.00	0.06
5	42.0	M	77.0	0.33	0.31	0.34	0.00	0.00	0.00
6†	53.0	M	95.0	0.35	0.38	0.35	0.50	0.02	0.00
7	54.0	M	95.0	0.26	0.30	0.33	0.05	0.00	0.00
8	52.0	F	60.0	0.40	0.30	0.32	0.11	0.00	0.06
9	63.0	F	40.0	0.51	0.62	0.63	0.23	0.00	0.00
10†	58.0	M	82.0	0.64	0.42	0.34	0.00	0.00	0.00
11	45.0	M	82.0	0.40	0.34	0.34	0.00	0.00	0.00
12	65.0	M	55.0	0.26	0.31	0.30	0.00	0.00	0.00
N = 12	53.0	F = 5	67.0	0.39	0.42	0.45	0.10	0.01	0.02
± s.e.mean		M = 7		±0.03	±0.05	±0.05	±0.04	±0.003	±0.009
P Value (compared to baseline)				—	>0.05	>0.05	—	≤0.05	≤0.05
P Value (compared to before pancuronium)				—	—	>0.05	—	—	>0.05

* Patient had a marked rise in Pa_{CO_2} during the study.

† Patient received intravenous sodium nitroprusside infusion throughout the study.

Table 2

Direct arterial blood pressure and heart rate changes following diazepam-ketamine-pancuronium in cardiac patients.

No.	Blood pressure in mmHg						Heart rate/min		
	Baseline		After diazepam-ketamine		After pancuronium				
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Baseline	After diazepam-ketamine	After pancuronium
1	135	55	155	60	155	70	75	72	82
2	145	65	145	75	164	105	75	82	126
3	95	50	95	50	105	60	65	61	72
4	115	65	110	70	120	75	78	69	81
5	130	75	175	115	170	105	72	66	76
6	180	75	155	75	170	85	69	96	123
7	155	85	125	75	150	100	57	51	60
8	140	85	155	95	150	95	87	91	110
9	200	60	200	65	215	75	102	96	100
10	180	95	200	100	170	85	78	71	87
11	115	50	135	60	135	65	98	81	95
12	115	35	125	45	130	50	67	69	70
N = 12	142.0	66.0	148.0	74.0	153.0	81.0	77.0	75.0	90.0
±s.e.mean	9.14	5.04	9.44	5.97	8.30	5.22	3.8	4.0	6.0
P Value (compared to baseline)	—	—	>0.05	≤0.05	>0.05	≤0.01	—	>0.05	≤0.05
P Value (compared to before pancuronium)	—	—	—	—	>0.05	>0.05	—	—	≤0.001

alter the statistical significance. Patient #2 showed the greatest increases in systolic (15%) and diastolic (40%) arterial pressures (Table 2). The mean increases for the group were 3.7% for systolic pressure and 9.0% for diastolic pressure. Decreases greater than 10% in systolic and diastolic arterial blood pressures occurred only in patient #10 who showed a 15% decrease in both, presumably due to an i.v. infusion of sodium nitroprusside.

(4) *Arterial blood gases*: Arterial P_{O_2} was maintained over 290 mmHg in all the patients during the study. Mean arterial P_{CO_2} was 38.5 $\pm$4.3 mmHg prior to induction, 37.5$\pm$7.5 mmHg after induction but prior to pancuronium, and 37.3$\pm$8.2 mmHg 5 min after pancuronium administration. In patient #2, Pa_{CO_2} rose from a resting level of 39.4 mmHg to 47.8 mmHg following induction of anesthesia, and further to 54.6 mmHg 5 min after pancuronium administration.

(5) *ECG changes*: No arrhythmia occurred following the administration of pancuronium.

(6) *Complications*: No bronchospasm or evidence of allergic reactions occurred in any of the patients.

DISCUSSION

The absence of a significant increase in plasma free-norepinephrine and epinephrine, in combination with the absence of an increase in blood pressure following pancuronium, indicates that no *marked* increase in sympathetic tone was induced by the intravenous administration of a full paralyzing dose of pancuronium in this group of cardiac patients. This is in contrast to the reported increase in catecholamines by NANA et al. (1973). With the exception of patients #3 and #9, normal autonomic tone was present prior to anesthetic induction with diazepam-ketamine in most cardiac patients, as evidenced by their normal plasma free-norepinephrine concentrations and heart rates (Tables 1 and 2). Our observed mean norepinephrine level, adjusted to the mean age, is in agreement with the expected norepinephrine concentration of normal and hypertensive patients reported by LAKE et al. (1977). It is interesting to observe that even patients #3 and #9 did not have a significant elevation in norepinephrine concentrations following pancuronium administration. A marked increase in norepinephrine concentration occurred only in patient #2, who had airway obstruction and inadequate ventilation throughout the study, resulting in a marked increase in Pa_{CO_2} from 47.8 mmHg to 54.6 mmHg, which might have resulted in autonomic stimulation. A concomitant marked rise in plasma free-epinephrine further corroborates our assumption that the marked rises in norepinephrine concentration, blood pressure and heart rate in this patient were the result of adrenomedullary stimulation caused by the rapid rise in Pa_{CO_2} and the development of a marked base deficit (BE = -5.4 mEq).

That the diazepam-ketamine induction sequence might have influenced our findings may be discounted, since (1) the norepinephrine concentrations before induction and before pancuronium administration did not differ significantly, and (2) the expected increase in catecholamines occurred in patient #2 in prompt response to an increase in Pa_{CO_2}. The possibility that a sympathomimetic effect of pancuronium may be modified by diazepam cannot be ruled out completely. However, the observed lack of increase in norepinephrine and epinephrine definitely rules out a *marked* increase in sympathetic tone in this group of patients.

The possibility that pancuronium causes sympathetic stimulation in patients who suffered major injuries or who are in hemorrhagic shock, such as those in the study of NANA et al. (1973), cannot be ruled out by our findings. Since 40% of the patients of NANA et al. (1973) underwent emergency surgery, it was not unexpected that the resting norepinephrine and epinephrine levels were abnormally elevated, reflecting a major disturbance in

autonomic function prior to pancuronium injection. The large standard deviations in baseline catecholamines in their study certainly suggest that. Further, since no blood-gas determinations were done in their studies, the changes in norepinephrine and epinephrine concentrations could have been caused by hypercarbia and/or inadequate anesthesia.

The statistically significant increase in heart rate following pancuronium injection in our study is comparable to that observed by FOLDES et al. (1971) in unanesthetized healthy volunteers and to the reported rises in patients anesthetized with a wide variety of agents (SELLICK 1970, SMITH et al. 1970, SAXENA & BONTA 1971, BROWN et al. 1973).

The two main ways by which pancuronium may cause the observed tachycardia are: (1) sympathetic stimulation, as suggested by NANA et al. (1973) and more recently DOMENECH et al. (1976), or (2) inhibition of the cardiac muscarinic receptors, as proposed by SAXENA & BONTA (1971). Our inability to show a statistically significant rise in plasma free-norepinephrine following pancuronium in the present series would tend to favor the latter. Further evidence against increased sympathetic activity as a possible cause of tachycardia are the previous findings of VENDSALU (1960), KELSCH et al. (1971) and ZSIGMOND et al. (1972) that when central sympathetic stimulation leads to tachycardia, a prompt significant increase in norepinephrine concentration is consistently observed. However, an action of pancuronium on the postganglionic nerve endings causing a release of norepinephrine as proposed by DOMENECH et al. (1976) cannot be ruled out. Our study design does not permit the distinct differentiation between these possible mechanisms of action of pancuronium on heart rate.

Conclusion: Pancuronium does not increase mean plasma free-norepinephrine and epinephrine levels when given intravenously following induction of anesthesia with diazepam and ketamine in cardiac surgical patients, indicating that the observed increase in heart rate is more likely to be the result of the inhibition of the muscarinic receptors in the heart. Nonetheless, the significant tachycardia elicited by pancuronium in some cases should be considered when this agent is chosen as a muscle relaxant for intubation in cardiac patients.

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